Tumour markers in rheumatoid arthritis-associated interstitial lung disease

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Abstract

Objective

Interstitial lung disease (ILD) is the most common pulmonary extra-articular manifestations of rheumatoid arthritis (RA), but the pathogenesis of RA-ILD is unknown. The purpose of this study was to investigate the tumour markers levels in patients of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) and to explore the diagnostic value of serum tumour markers for RA-ILD.

Methods

Twenty-eight patients with RA-ILD and 83 patients with RA only were included. Serum levels of tumour markers carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 15-3, CA125, and CA19-9 were measured.

Results

Tumour markers CA15-3, CA125 and CA19-9 were increased in RA-ILD patients compared with RA without ILD patients. Logistic regression analysis revealed that older age (OR=1.06, 95% CI=[1.02–1.11]) and higher CA125 (OR=1.03, 95% CI=[1.01–1.05]) related to the increased risk of RA-ILD. ROC curve analysis showed the relationship between CA125 and RA-ILD was moderate (area under ROC curve (AUC)=0.78, 95% CI=[0.68–0.88]). In addition, CA125 levels above the normal reference (<35 U/ml) raised the risk of RA-ILD (OR=6.00, 95% CI=[2.37–15.16]).

Conclusion

RA patient with older age and elevated tumour markers especially CA125 levels should be evaluated to check whether there is a potential of ILD.

Key words

interstitial lung disease, rheumatoid arthritis, tumour marker

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterised by the joint inflammation. Extra-articular manifestations (ExAM) predominately involved in the heart, vascular, and pulmonary system and contribute to the excess mortality and morbidity of RA patients (1, 2). Interstitial lung disease (ILD), as the most common pulmonary extra-articular manifestations of RA, caused a significantly increased morbidity and mortality in RA patients (3). The prevalence of clinically significant ILD has been estimated in approximately 8-10% of subjects (3, 4), whereas an earlier autopsy study reported a prevalence of nearly 35% (5). An inception cohort study indicated a short survival (median, 3 years) after diagnosis of RA-ILD (6). Another inception study followed up to 18 years noted that excess mortality was seen in ILD (4%) (7). However, the aetiology and pathogenesis of RA with ILD remains unclear.

Tumour markers, which are substantially produced by malignant cells and can be used for screening or monitoring cancer progress, are elevated in patients of RA or ILD. An observational cohort study of 100 RA patients and controls noted that serum levels of tumour markers carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were increased in patients of RA. The elevated tumour marker levels were not related to disease activity or the presence of actual cancer (8). Moreover, patients of ILD were found to have significantly higher CEA and CA125 levels when compared with controls, and the increased CEA and CA125 levels might predict increased risk of cancer (9). Thus, a potential role of tumour biomarkers in RA-ILD caught much attention.

The current study aimed to investigate the tumour marker levels in RA-ILD and RA without ILD, and to explore the diagnostic value of serum tumour markers for RA-ILD.

Methods

Study subjects

Patients with a confirmed diagnosis of RA were selected from the clinical database between 2011 and 2014. A diagnosis of RA was made by at least two rheumatologists according to the American College of Rheumatology (ACR) 1987 criteria (10). High resolution computed tomography (HRCT) imaging abnormalities indicative of ILD were evaluated by two blinded radiologists and a pulmonologist. Patients with one or more imaging characteristics, including traction bronchiectasis, reticular abnormalities, and honeycombing, and/or ground glass opacification, were identified as radiographically defined RA-ILD (11). Demographics features, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) levels, and tumour marker levels were extracted from the database. Patients with a diagnosis of cancer or neoplasm were excluded. The study protocol was approved by the Institutional Review Board of West China Hospital of Sichuan University, and written informed consent was obtained from all subjects.

Tumour markers

Tumour markers including CEA, CA15-3, CA19-9 and CA125 were measured electro-chemiluminescence immunoassay using Roche modular analytics E170 (F. Hoffmann-La Roche Ltd., Basel, Switzerland) in the Central Lab at West China Hospital. The normal ranges of each tumour biomarkers are presented as follows: CEA <3.4 ng/ml, CA15-3 <21 U/ml, CA19-9 <22 U/ml, CA125 <35 U/ml.

Statistical analysis

Continuous data was reported as mean ± SD for normally distributed data or the median (range) for non-normally distributed data. Categorical data was reported as frequencies. Continuous data was analysed by using independent samples *t*-test or Mann-Whitney U-test. Categorical data was analysed by using chi-squared test. Logistic regression analysis was performed to evaluate the strength of association between RA-ILD and tumour biomarkers. Receiver operating characteristic (ROC) curve was generated to analyse the discriminatory power for each tumour biomarker. Data was analysed by using the SPSS 21.0 software (SPSS Inc., Chi-

cago, IL, USA) and a two-sided *p*-value below 0.05 was regarded as statistically significant.

Results

Patients' characteristics

A total of 111 RA patients were included and these patients were further classified into RA-ILD (n=28) or RA without ILD (n=83) group, which showed a prevalence of RA-ILD was 25%. Characteristics of the included patients were presented in Table I. The mean ± SD age of the RA-ILD group was 63.36±11.26 and that of RA without ILD group was 54.10±15.52. Patients with RA-ILD were older than patients without ILD (p=0.001). Increased RF levels were observed in RA-ILD patients (p=0.005). There was no significant difference in sex, smoking status, medication and Anti-CCP levels between the two groups. Forty-two patients underwent pulmonary function test. Twenty-five of them were in the RA-ILD group and the rest 17 were in the RA without ILD group. Airflow limitation (FEV1/FVC <70%) was detected in 7/25 (28%) patients in the RA-ILD group and 3/17 (18%) patients in the RA without ILD group.

Tumour markers

Serum levels of CA15-3 (p=0.002), CA125 (p<0.001) and CA19-9 (p=0.020) were elevated in patients with RA-ILD compared with patients without ILD. No significant difference was observed in CEA (p=0.071). The logistic regression analysis was performed to find the association between tumour markers and RA-ILD. The forward stepwise model included pre-assigned covariates that reached a significance level of 0.05. Age, RF levels, CA15-3, CA125, and CA19-9 were included in this model. The results observed that age (beta 1.06, 95% CI=[1.02–1.11]) and CA125 (beta 1.03, 95% CI=[1.01–1.05]) were significantly associated with RA-ILD, suggesting older age and higher CA125 levels increased the risk of RA-ILD (Table II).

A ROC assessment was performed to detect the diagnostic value of CA125 for RA-ILD. There was a significant association between higher values of CA125 and RA-ILD. Area under ROC curve (AUC) for detection of RA-ILD was 0.78 (95% CI=[0.68–0.88]) (Fig. 1). Using the normal reference value of CA125 level (<35 U/ml) as a cut-off, sensitivity for discriminating RA patients with or without ILD was 60.71%, and specificity was 79.52%. Also, values above the normal reference level (35U/ml), raised the risk of RA-ILD (OR=6.00, 95% CI=[2.37–15.16]).

Table I. Characteristics of included patients of RA with or without ILD.

	RA without ILD	RA with ILD	*p*-value
n	83	28	
Age, years	54.10 ± 15.52	63.36 ± 11.26	0.001
Sex, male/female	30/53	16/12	0.051
Smoking status			0.175
Never	60	15	
Fomer	13	7	
Current	8	6	
Unknown	2	0	
Medication used			
Corticosteroid	59 (71.8%)	19 (67.86%)	0.747
Methotrexate	48 (57.83%)	19 (67.86%)	0.348
Meloxicam	44 (53.01%)	18 (64.29%)	0.299
RF	113.00 (20.00, 3830.00)	520.50 (20.00, 4520)	0.005
Anti-CCP	255.20 (7.00, 500.00)	296.45 (2.00, 500.00)	0.551
Tumour markers			
CEA	1.62 (0.20, 5.74)	2.06 (0.57, 11.40)	0.071
CA15-3	13.04 (4.90, 47.59)	15.84 (8.99, 93.95)	0.002
CA125	21.16 (4.60, 205.60)	38.34 (12.60, 199.80)	<0.001
CA19-9	8.02 (0.60, 153.10)	13.90 (0.60, 355.00)	0.020

RA: rheumatoid arthritis; ILD: interstitial lung disease; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; CEA: carcinoembryonic antigen; CA: carbohydrate antigen.

Table II. Logistic regression analysis of the association of RA-ILD and tumour markers.

Variate	OR	95% CI	*p*-value
Age	1.06	1.02-1.11	0.006
CA125	1.03	1.01-1.05	0.003

CA: carbohydrate antigen; OR: odds ratio; CI: confidence intervals.

Discussion

The present study has investigated the association between RA-ILD and tumour markers. Serum tumour markers CA15-3, CA125 and CA19-9 were observed higher in patients with RA-ILD than patients with RA. Logistic regression analysis found that older age and higher CA125 levels were significantly associated with increased risk of RA-ILD. The diagnostic accuracy of CA125 for RA-ILD was moderate, and above a cut-off value of normal reference was a risk factor for RA-ILD. These observations suggested that abnormal tumour marker levels especially increased CA125 levels could be suggestive of ILD in patients of RA. Pulmonary diseases were found to account for a mortality of 10-20% in patients of RA (12, 13). ILD is classified as sever ExAM due to its role in worsening prognosis in patients of RA (3, 6). The reported prevalence of ILD in RA patients varied among studies, which is partly due to a lack of clear consensus in diagnosis criteria, diagnosing tools used, or descriptions in papers. Clinical presentation, blood gases, pulmonary function tests and HRCT scan are often used to evaluate ILD. Previous studies reported that the prevalence of ILD was 19–44% in patients of RA (3, 14, 15). Recently, transthoracic ultrasound of the lung also showed potential value in detecting incipient pulmonary structural changes in patients with RA (16, 17). Similarly, the present study observed a prevalence of 25%. However, a large part of patients with RA-ILD had no respiratory symptoms such as dyspnea or cough, which could make

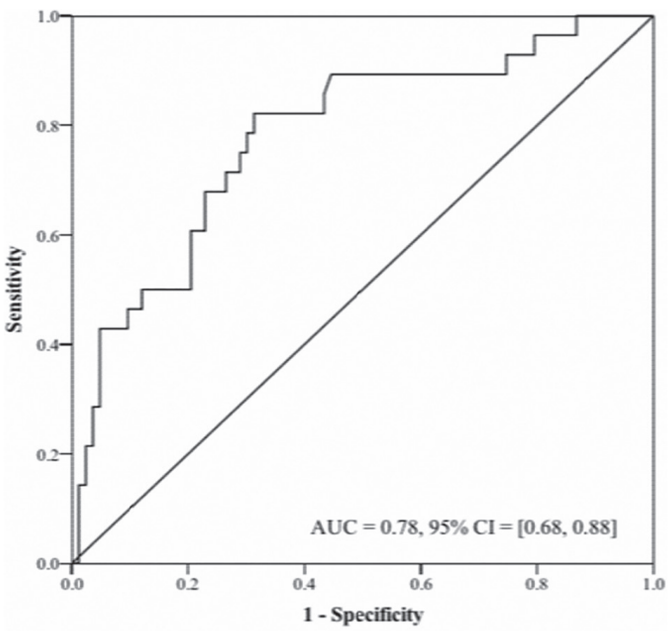

Fig. 1. The predictive capacity of levels of CA125 for the presence of RA-ILD.

a underestimate of the prevalence (18). Although lung biopsy is regarded as a better tool for the diagnosis of ILD in patients of RA, it is only adopted very occasionally due to its invasion.

RA-ILD is found to be associated with genetic (19-21), environmental factors (22), and some treatment drugs, such as methotrexate (23), but the exact aetiology underlying RA-ILD remains unclear. Saag *et al*. reported that cigarette smoking was an independent risk factor of the development of RA-ILD, and pack-years of cigarette smoking were inversely associated of DLCO value (24). However, Ayhan-Ardic's study indicated that smoke exposure is not a requirement for the development of ILD in RA patients (25).Patients with RA-ILD often observed with older age (26, 27), and older age was found to be a significant predictor of mortality in patients with RA-ILD (28). Mori *et al*. reported that age over 65 years increased the risk of ILD in RA patients more that four-fold (29). High level of RF and anti-CCP antibodies were reported to be associated with increased risk of ILD in patients of RA (30). In another study, higher RF levels (>100 IU/ml) was reported significantly associated with increased risk of ILD, whereas anti-CCP was not (29). This was consistent with the results reported by Bongartz (31). Although RF levels were observed higher in patients of RA-ILD compared with patients of RA here, no significant association between RF levels and risk of RA-ILD was found in the logistic regression analysis. Further studies are warranted to address whether these antibodies contribute to the incidence of ILD in RA patients.

The relationship between tumour markers and RA or ILD is still unknown. Tumour markers are substantially produced by tumour cells and elevated levels of them often indicate the presence of cancer. However, tumour markers were observed increased in other benign conditions. Patients with RA were associated with increased CA19-9, CA125 and CA15-3 (32). Another observational cohort study showed a similar result that patients with RA had high levels of CEA and CA19-9 even with controlled inflammatory activity (8). Yamamoto reported that with ILD increased the expression of CA19-9 and this elevation could reverse after treatment with immunosuppressant (33). Another study conducted by Dai *et al*. also observed an increased CEA and CA125 levels in ILD without cancer patients (9). The present study has observed higher levels of CA15-3, CA125 and CA19-9 in patients of RA-ILD, similar to our smaller sample size study (34), suggesting a potential role of tumour markers in RA-ILD. However, the logistic regression analysis only found CA125 was independently associated with RA-ILD. Considering CA125 was found to be associated with specific types of cancer or other benign conditions, the potential role of CA125 for early detection of RA-ILD should be further tested.

Some limitations should be mentioned. Firstly, because this was a retrospective study, we were unable to analyse whether there was casual association between tumour markers and the development of ILD in patients with RA. Also, we were unable to follow these patients to examine the clear relationship between the elevated levels of tumour makers in patients of RA-ILD and the risk of cancer. Secondly, the relatively small number of RA-ILD patients may bring selection bias. Thirdly, diagnosis of ILD with lung biopsy is unavailable. Longitudinal studies with larger sample size are needed to explore the actual relationships between RA-ILD and tumour markers.

In summary, serum CA15-3, CA125 and CA19-9 levels are elevated in patients of RA-ILD compared with patients of RA. Older age and higher levels of CA125 are significantly associated with increased risk of ILD in patients with RA in logistic regression analysis. Even with limited sensitivity and specificity, RA patient with older age and elevated tumour markers should be evaluated to check whether there is a potential of ILD.

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