Serum Oncomarkers In Patients With MPO-ANCA-Positive AAV: Diagnostic And Prognostic Predictive Values For Interstitial Lung Disease

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Title page

Serum oncomarkers in patients with MPO-ANCA-positive AAV: diagnostic and prognostic predictive values for interstitial lung disease

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Abstract

Purpose: To explore in myeloperoxidase anti-neutrophil cytoplasmic antibody-positive anti-neutrophil cytoplasmic antibody-associated vasculitis (MPO-AAV) the value of circulating oncomarkers in identifying interstitial lung disease (ILD) and predicting prognosis.

Methods: Newly diagnosed MPO-AAV patients were recruited retrospectively at a single center.

The serum levels of carbohydrate antigen (CA) 19-9, CA125, cytokeratin fraction 21-1 (CYFRA21-1), carcinoembryonic antigen, squamous cell carcinoma antigen and neuron-specific enolase were compared between patients with and without ILD. The strength of the oncomarkers in identifying ILD was assessed through logistic regression and receiver operating characteristic (ROC) curves. Correlation analysis was applied to detect the associations between oncomarkers and ILD severity. The significance of serum oncomarkers as prognosis predictors for MPO-AAV associated ILD was evaluated by survival analysis.

Results: 169 MPO-AAV patients were included and ILD was found in 101 patients. Serum CA125, CA19-9 and CYFRA21-1 were significantly higher in patients with ILD than those without ILD. The area under the ROC curve of CA19-9, CA125, and CYFRA21-1 for identifying ILD was 0.701, 0.660, and 0.711, respectively. A specificity of 98.5% for diagnosing ILD was found for CA19-9 at the recommended normal level. CA19-9 was positively correlated with HRCT fibrosis score ($r = 0.498$, $p < 0.001$) and CYFRA21-1 was correlated with ground-glass score ($r = 0.316$, $p = 0.002$). Both CA19-9 and CYFRA21-1 were independent risk factors for all-cause mortality in patients with ILD.

Conclusion: Serum CA19-9 and CYFRA21-1 maybe useful markers in the diagnosis, disease severity evaluation and prognosis prediction of MPO-AAV associated ILD.

Keywords

Anti-neutrophil cytoplasmic antibody-associated vasculitis, myeloperoxidase, oncomarkers, interstitial lung disease, diagnosis, prognosis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an idiopathic autoimmune disease, which is characterized by the presence of anti-neutrophil cytoplasmic autoantibodies (ANCA) and systemic vasculitis, and predominantly affects small-caliber blood vessels [1]. The two most relevant antigens of ANCA are proteinase 3 and myeloperoxidase (MPO). Interstitial lung disease (ILD) is one of the most common types of lung involvement in AAV and is primarily associated with myeloperoxidase (MPO)-ANCA. As reported previously, ILD is significantly correlated with poor prognosis in AAV patients [2,3]. A recent meta-analysis of ten retrospective cohort studies yielded a pooled risk ratio of 2.90 for death among those with AAV-ILD compared to the control group [4].

Oncomarkers, known as tools for screening tumors and monitoring progression, are usually abnormally increased in patients with malignant diseases. However, they are not specific to tumor cells, the elevation of oncomarkers, especially those released by epithelial cells, has also been observed in idiopathic pulmonary fibrosis (IPF) patients, and their correlations with disease severity, functional decline, and prognosis have been discovered [5,6].

Similar mechanisms appear to be involved in the development of pulmonary fibrosis in IPF and connective tissue disease-related interstitial lung diseases (CTD-ILDs) [7-9]. The biomarkers found in IPF, including Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D), have shown comparable value in CTD-ILDs [10], yet the expression and values of various oncomarkers in AAV-ILD have not been explored before. In the present study, we aimed to evaluate the possible association between circulating oncomarkers and ILD in patients with MPO-AAV and their prognostic

predictive values.

Methods

Study design and patient selection

This was a single-center retrospective cohort study. Newly diagnosed MPO-AAV inpatients with thoracic high-resolution computed tomography (HRCT) and results of circulating oncomarkers at the time of diagnosis including CA19-9, CA125, cytokeratin fraction 21-1 (CYFRA21-1), CEA, squamous cell carcinoma antigen (SCC-Ag), and neuron-specific enolase (NSE), were consecutively recruited from January 2012 to December 2019 at Beijing Chao-Yang Hospital, China, a regional medical center specializing in ILDs. AAV diagnosis was based on the 2012 Chapel Hill Consensus Conference criteria and the European Medicines Agency algorithm [1,11]. Serum levels of MPO-ANCA were analyzed by commercial anti-MPO-hn-hr enzyme-linked immunosorbent assay (ELISA) (EUROIMMUN, Lübeck, Germany) in accordance with the manufacturer's instructions, ≥ 20 relative units/ml (RU/ml) was identified as positive. HRCT imaging abnormalities indicative of ILD were evaluated by two ILD experts (Ye and Zhan) who were blinded to the clinical data. Any disagreements were resolved in the presence of a third expert on respiratory diseases. Patients were excluded for the following reasons: 1) concomitant lung cancer or other malignancies, or a history of malignancy; 2) concomitant disease that could result in ILD, such as other CTDs, pneumoconiosis, or a history of dust exposure; 3) active infection at diagnosis; 4) eosinophilic granulomatosis with polyangiitis (EGPA); and 5) incomplete data or loss to follow-up. The study was conducted in accordance with the World Medical Association Declaration of Helsinki (revised in 2013) and was approved by the Ethics Committee of Beijing Chao-Yang Hospital.

Data collection and follow-up

The patients' medical records were reviewed to extract clinical data uniformly at the first clinical visit. The demographics included age, sex, body mass index (BMI), and smoking status. Laboratory findings included the oxygenation index (OI; calculated as the ratio of arterial partial oxygen/inspired oxygen fraction), C-reactive protein (CRP), alanine transaminase (ALT), serum creatinine (Scr), and oncomarkers. The concentration of circulating oncomarkers was determined by electrochemiluminescence immunoassay using a Roche Hitachi Cobas (Hitachi, Tokyo, Japan). The recommended normal ranges of each marker are as follows: CA19-9 ≤ 37.00 U/ml; CA125 ≤ 35.00 U/ml; CYFRA21-1 ≤ 2.08 ng/ml, CEA ≤ 5 ng/ml; SCC-Ag ≤ 1.5 ng/ml; and NSE ≤ 16.3 ng/ml. The percentage predicted forced vital capacity (FVC%) and percentage predicted single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB%) were collected as parameters for pulmonary function. Disease activity at diagnosis was assessed using the Birmingham Vasculitis Activity Score (BVAS) version 3 [12]. The initial regimens for induction remission were also recorded.

HRCT score system

High-resolution 0.625-mm-thick CT sections of the lungs were performed in all patients and scored by Ye and Zhan according to the method proposed by Kazerooni et al. [13]. Briefly, three images taken at the level of the aortic arch, the carina, and 1 cm above the diaphragm were scored for both ground-glass opacity and fibrosis (reticulation and honeycombing) on a scale of 0-5, depending on the percentage of each lobe involved. The scores for each lobe were averaged for both readers, and the average score was summed as the HRCT score.

Follow-up strategy

The primary endpoint was all-cause mortality from the time of diagnosis to May 2020. We scheduled a follow-up every 6 months. Vital status was acquired from a review of the patients' medical records and follow-up phone calls to the patients or their family members.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 23 (IBM Inc., Chicago, IL, USA). The intergroup differences for continuous data were analyzed using an independent-sample t-test or Mann–Whitney U test, and categorical data were analyzed using the chi-square test. Logistic regression and receiver operating characteristic (ROC) curves were used to evaluate the strength of oncomarkers in identifying ILD in MPO-AAV and the optimal threshold. The Spearman rank test was used for correlation analysis. The impact of the predictor variables on mortality was assessed using univariable and multivariable Cox regression analyses. Statistical significance was set at $P < 0.05$.

Results

Population characteristics

A total of 169 MPO-AAV patients were ultimately included in the analysis; 101 patients had MPO-AAV with ILD and 68 had MPO-AAV without ILD. As summarized in Table 1, the mean age of the entire cohort was 68.2 ± 10.8 years, 85 (50.3%) patients were male, and 80 (47.3%) had a smoking history. The median (IQR) for BVAS was 14.5 (12.0-20.0). Compared to patients without ILD, those with ILD were older ($p = 0.003$), more likely to be male ($p = 0.028$), had more frequent smoking history ($p = 0.005$), and lower BVAS ($p < 0.001$) and CRP ($p = 0.013$) levels. Both groups were

comparable in terms of BMI, OI, ALT, and Scr levels at diagnosis. Patients with ILD had a median FVC% of predicted as 88.1 (76.9-107.4) and DLCO-SB% of predicted as 53.9 (41.1-67.6). The median calculated HRCT ground-glass score and fibrosis score in these patients were 2.0 (0-5.5) and 4.5 (3.0-7.0), respectively. For induction treatment, 160 (94.7%) patients were administered glucocorticoids, 121 (71.6%) received immunosuppressants, and no statistical differences were found in the induction treatment methods between the two groups. The median follow-up duration was 22.7 (2.8-51.2) month for patients with ILD and 30.3 (13.1-62.9) month for those without ILD.

Oncomarker levels and the diagnostic value for ILD in MPO-AAV

In the entire study population, serum levels over normal ranges were observed for CA19-9 in 34 (20.1%), CA125 in 68 (40.2%), CTFRA21-1 in 95 (56.2%), CEA in 16 (9.5%), SCC-Ag in 52 (30.8%), and NSE in 40 (23.7%) patients. Patients with ILD presented with significantly higher serum CA19-9 (median, 18.0 versus 12.2 U/ml, $p < 0.001$), CA125 (median level 36.0 vs. 19.5 U/ml, $p < 0.001$), and CYFRA21-1 (median level 2.9 vs. 1.9 ng/ml, $p < 0.001$) than those without ILD. The frequencies of the three markers abnormally elevated in patients with ILD were also significantly higher. Both serum levels and over-range frequencies for CEA, SCC-Ag, and NSE were comparable between the two groups (Table 2).

When the recommended normal reference level was used as a threshold, CA19-9 (odds ratio (OR), 24.345; 95% CI = 3.025-51.254; $p = 0.003$), CA125 (OR, 3.795; 95% CI = 1.694-8.501; $p = 0.001$), and CYFRA21-1 (OR, 2.994; 95% CI = 1.422-6.302; $p = 0.004$) higher than the threshold were significantly associated with ILD after adjustment of age, sex, smoking history and BMI. The sensitivity and specificity of CA19-9, CA125 and CYFRA21-1 for identifying ILD in patients with

MPO-AAV was 32.7% and 98.5%, 50.5% and 75.0%, 67.3% and 60.3%, respectively. The area under the ROC curve of the three markers was 0.701 (95% CI = 0.624-0.778), 0.660 (95% CI = 0.576-0.744), and 0.711 (95% CI = 0.631-0.792) (Figure 1).

Correlations between oncomarkers and severity of lung involvement in patients with MPO-AAV and ILD

In patients with MPO-AAV and ILD, correlation analysis revealed that the serum CA19-9 levels were negatively correlated with DLCO-SB% predicted (r = -0.402, p = 0.018) and OI (r = -0.364, p = 0.001) and positively correlated with HRCT fibrosis score (r = 0.498, p < 0.001). Serum CA125 levels were also adversely correlated with DLCO-SB% predicted (r = -0.363, p = 0.035) and OI (r = -0.296, p = 0.015). Serum CYFRA21-1 levels correlated positively with HRCT ground-glass score (r = 0.316, p = 0.002) and negatively with OI (r = -0.342, p = 0.005) (Table 3).

Oncomarkers in predicting prognosis for patients with MPO-AAV and ILD

According to univariate analysis, age, initial BVAS, Scr, CA19-9, and CYFRA21-1 levels at diagnosis were significantly associated with an increased risk of death in patients with MPO-AAV with ILD, while immunosuppressants for induction therapy were a protective factor (Table 4). After adjustment for covariates, CA19-9 (hazard ratio (HR): 1.003, p = 0.010) and CYFRA21-1 (HR: 1.028, p = 0.002) were still risk factors for all-cause mortality.

Discussion

The present study investigated the possible value of circulating biomarkers for identifying ILD in patients with MPO-AAV and predicting outcomes. Among the oncomarkers detected, CA125, CA19-9

and CYFRA21-1 were significantly associated with ILD. CA19-9 at the recommended normal range had a high specificity in identifying ILD for MPO-AAV. Both CA19-9 and CYFRA21-1 were independent predictors of all-cause mortality in MPO-AAV associated ILD.

To date, the pathogenic mechanisms of AAV-ILD have not been fully elucidated. It is generally considered that in patients with CTD, inflammation is one of the earliest events of ILD occurrence. The influx of inflammatory cells into the interstitial and alveolar airspaces causes epithelial damage, and repetitive cycles of bronchoalveolar epithelial injury lead to final lung fibrosis [14]. However, ILD does not occur in all patients with CTDs, and it is critical to identify ILD in patients with AAV at an earlier stage considering the adverse impact of ILD on the prognosis. In the present study, we observed significantly higher levels of CA19-9, CA125, and CYFRA21-1 in MPO-AAV patients with ILD than in those without ILD. This may reflect the alterations of lung epithelial cells involved in AAV-ILD given that the three associated oncomarkers originated from the epithelium. CA19-9 and CA125 (also termed MUC16) are both mucin-associated carbohydrate antigens, which are synthesized and secreted by epithelial cells of the central airways and/or respiratory glands in normal lung tissues, but with no expression in the alveolar epithelium [15]. Maher et al. previously identified the increased expression of CA19-9 and CA-125 throughout the metaplastic epithelium in fibrotic lesions of patients with idiopathic pulmonary fibrosis (IPF), and this localization was associated with mucous secretion, which was particularly apparent within honeycomb cysts [16]. MUC16 transcript and MUC16 protein expression levels were also shown to be higher in lung tissue from patients with IPF than in healthy subjects, and were localized in fibroblasts and hyperplastic alveolar type II cells [17]. In our study, the serum levels of CA19-9 and CA125 were significantly correlated with the DLCO-SB% predicted,

CA19-9 also had a correlation with HRCT fibrosis score, indicating that pulmonary fibrosis tissue may be associated with the elevation of these markers. It is possible that the CA19-9 and CA125 produced by the metaplastic epithelium become concentrated in the mucus, and then transfer into the blood through the injured epithelial barrier, resulting in elevated levels in the sera of patients with ILD. CYFRA 21-1 is a water-soluble cyto-keratin-19 fragment with a cytoskeletal structure, expressed on type 1 and 2 pneumocytes and respiratory bronchiolar epithelial cells in normal lungs [18]. When lung epithelial cells are injured, CYFRA21-1 is released, resulting in its elevation in BALF and serum levels [19]. Meanwhile, inflammatory cells and cytokines can promote the release of CYFRA21-1 [20,21]. The significant correlation between serum CYFAR21-1 levels and HRCT ground-glass scores shown in our patients is concordant with these previous findings.

We next assessed the ability of the serum CA19-9, CA125, and CYFRA21-1 levels to be used in identifying ILD in patients with MPO-AAV and predicting prognosis. The results demonstrated that the three markers had moderate value in diagnosing ILD. However, a specificity as high as 98.5% for CA19-9 in identifying ILD at the recommended normal range was observed. Only one patient (1.5%) in the non-IP group had a serum CA19-9 level > 37 U/ml, while the percentage in healthy individuals was 0.6% [22]. Consequently, if a patients with MPO-AAV had abnormally elevated CA19-9 levels, concomitant ILD can be considered probable. Therefore, in the presence of elevated serum CA19-9 levels, it is imperative to carefully screen for ILD in patients with MPO-AAV. In addition, the three oncomarkers, especially CA19-9 and CYFRA21-1 might have values in evaluating disease severity and guiding treatment for AAV-ILD, since the correlations between CA19-9 and lung fibrosis score, CYFRA21-1 and lung inflammation score, and both of the two markers and OI were found. In patients

with MPO-AAV with ILD, the initial levels of CA19-9 and CYFRA21-1 were independent predictors of all-cause mortality in our cohort. Lung fibrosis is regarded as one of the determinants of prognosis in CTDs, including AAV [2]. A high degree of inflammation is associated with increased epithelial cell injury, and the degree of alveolar epithelial damage at the primary stage is a major determinant of the likelihood of progression of fibrosis [23,24]. The associations between initial levels of CA19-9 and CYFRA21-1 with outcomes of AAV-ILD are plausible, yet whether these oncomarkers are onlookers or players still requires further confirmation. The MUC family members, especially MUC1 (known as KL-6) and MUC5B, are considered as key effectors in cell growth and tissue remodeling processes compatible with the processes observed in lung fibrosis [25]. A recent study reported that the MUC16 overexpression in patients with IPF induced fibrotic responses mediated by the transforming growth factor-β1 canonical pathway [17], although the predictive value of CA125 was not found in our study.

As for CEA, a fetal glycoprotein originating from epithelial cells, previous studies have shown inconsistent outcomes. In a study from the UK, 51% of patients with IPF had a serum CEA concentration higher than the upper limit of the normal range, and the CEA level was significantly correlated with lung function and the extent of lung fibrosis [6]. Higher serum CEA levels in patients with pSS with ILD than in those without ILD have also been reported [26]. In contrast, Sargin et al. observed no statistical association between CEA and ILD in patients with RA [27]. According to our data, only a few AAV patients were shown to have abnormally elevated CEA levels, and no discrepancies were found between patients with and without ILD. Moreover, no correlations between lung involvement severity and prognosis of patients with ILD were found. The primary disease might be one of the reasons for the inconsistency between the studies, as indicated by a previous study from

our institution. CEA levels in patients with IPF were obviously higher than those in patients with CTD-ILD [28]. The expression of oncomarkers in various patterns of ILD should be further investigated.

In conclusion, we have demonstrated that circulating oncomarkers, especially CA19-9 and CYFRA21-1, are useful in diagnosing and evaluating disease severity and predicting prognosis in MPO-AAV patients with ILD. These markers are simple, cost-effective and routinely available, may be considered as candidate biomarkers for AAV-ILD assessment.

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions

Shuqiao Yang was responsible for completing the analysis of data and writing. Yali Fan and Ruimin Ma performed all data collection and the follow up. Xi Zhan, Jing Wang and Qiao Ye evaluated the chest images. Q Ye also contributed as primary investigator and was responsible for designing the study, recruiting the patients and writing the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Beijing Chao-Yang Hospital (Date 23 September, 2019/No 2019-D-484).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and material

The data used and analyzed in this study is included in the article or are available from the corresponding and first authors on reasonable request.

Figure Legends

Fig. 1 The ROC curves of CA19-9, CA125 and CYFRA21-1 for the presence of ILD in MPO-AAV patients. (a) CA19-9, (b) CA125, (C) CYFRA21-1. ROC, receiver-operating characteristic; CA, cancer antigen; CYFRA21-1, cytokeratin fraction 21-1; ILD, interstitial lung disease; MPO-AAV, myeloperoxidase anti-neutrophil cytoplasmic antibody-positive anti-neutrophil cytoplasmic antibody-associated vasculitis; AUC, area under curve; CI, confidence interval.

Figures

Figure 1

The ROC curves of CA19-9, CA125 and CYFRA21-1 for the presence of ILD in MPO-AAV patients. (a) CA19-9, (b) CA125, (C) CYFRA21-1. ROC, receiver-operating characteristic; CA, cancer antigen; CYFRA21-1, cytokeratin fraction 21-1; ILD, interstitial lung disease; MPO-AAV, myeloperoxidase anti-neutrophil cytoplasmic antibody-positive anti-neutrophil cytoplasmic antibody-associated vasculitis; AUC, area under curve; CI, confidence interval

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