Changes and clinical significance of serum tumor markers in patients with rheumatoid arthritis combined with interstitial lung disease

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ABSTRACT

Objective: To investigate the changes and clinical significance of serum tumor markers in patients with rheumatoid arthritis (RA) combined with interstitial lung disease.  
Methods: A total of 50 healthy volunteers were chosen as the normal control group, 47 patients with rheumatoid arthritis alone were chosen as the RA group, and 28 patients with rheumatoid arthritis combined with interstitial lung disease were chosen as combined disease group. The differences in the levels of serum tumor markers, RA markers and inflammatory mediators were compared among the three groups, and Pearson test was used to evaluate the correlation of serum tumor marker levels with RA markers and inflammatory mediators in patients with RA combined with interstitial lung disease.  
Results: Serum tumor markers CA199, CA153 and CEA levels of combined disease group were higher than those of RA group; RA markers RF and GPI levels were higher than those of RA group whereas CCP and AKA levels were not significantly different from those of RA group; inflammatory mediators HMGB1, GM-CSF, IL-6, IL-17 and IL-27 levels were higher than those of RA group. Correlation analysis showed that serum tumor markers CA199, CA153 and CEA levels in patients with RA combined with interstitial lung disease were positively correlated with RF, GPI, HMGB1, GM-CSF, IL-6, IL-17 and IL-27 levels.  
Conclusion: Serum tumor markers CA199, CA153 and CEA levels abnormally increase in patients with RA combined with interstitial lung disease, and the specific levels were directly correlated with the disease severity.

1. Introduction

Rheumatoid arthritis (RA) is a systemic disease mainly characterized by inflammatory synovitis, which mainly invasively involves hand and foot facet joints and even leads to joint deformity and afunction, and can also be associated with abarticular organ dysfunction(1,2). Interstitial lung disease (ILD) is one of the most serious complications of RA, it mainly involves the alveolar walls, small airway and capillaries, and many studies have confirmed that the treatment outcome of RA patients combined with ILD is mostly worse than that of patients with RA alone(3,4). Early determining whether patients with RA are combined with ILD and taking active treatment is the most reliable way to improve the patients’ condition and optimize the final treatment outcome, but there are no targeted diagnostic indicators for RA combined with ILD at present. Current research has shown that there might be different degrees of changes in serum tumor marker levels in patients with RA combined with ILD, it is expected to become an effective method for auxiliary diagnosis of the disease, but there is little related research at present. In this study, serum levels of tumor markers were compared between patients with different RA conditions, and the inner link between their levels and specific illness was further determined in order to clarify the application value of tumor markers in patients with RA combined with ILD.
2. Information and methods

2.1 Inclusion and exclusion criteria

Inclusion criteria: (1) meeting the clinical diagnostic criteria for RA and interstitial lung disease; (2) developing interstitial lung disease after RA onset; (3) not over 80 years old; (4) who or whose family members signed the informed consent form. Exclusion criteria: (1) combined with bacterial pneumonia, chronic obstructive pulmonary disease and other lung diseases; (2) combined with malignant tumor diseases; (3) combined with systemic lupus erythematosus, ankylosing spondylitis and other autoimmune disorders; (4) pregnant or breastfeeding women.

2.2 Case information and grouping

A total of 50 healthy volunteers were enrolled in normal control group, 47 patients with rheumatoid arthritis alone were enrolled in the RA group, and 28 patients with rheumatoid arthritis combined with interstitial lung disease were enrolled in combined disease group. There were 22 males and 28 females in the normal control group, and they were 38-69 old; there were 19 males and 28 females in the RA group, and they were 40-70 years old; there were 11 males and 17 females in the combined disease group, and they were 41-69 years old.

2.3 Serum tumor marker content detection

5.0 mL of morning fasting peripheral blood specimens were collected from the three groups of subjects to separate upper serum, and enzyme-linked immunosorbent assay method was used to determine the tumor markers carbohydrate antigen 199 (CA199), carbohydrate antigen 153 (CA153) and carcinoembryonic antigen (CEA).

Table 1. Comparison of serum tumor marker levels among the three groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>CA199</th>
<th>CA153</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>20.18±2.53</td>
<td>15.46±2.03</td>
<td>2.09±0.24</td>
</tr>
<tr>
<td>RA group</td>
<td>47</td>
<td>43.25±5.11*</td>
<td>50.18±5.47*</td>
<td>4.11±0.43*</td>
</tr>
<tr>
<td>Combined disease group</td>
<td>28</td>
<td>75.19±8.64*</td>
<td>98.27±10.16*</td>
<td>6.93±0.85*</td>
</tr>
</tbody>
</table>

Note: compared with control group, *P<0.05; compared with RA group, #P<0.05.

2.4 RA markers and inflammatory mediators

Peripheral blood serum specimens of the three groups of research subjects were also obtained, immunoturbidimetry was used to determine the levels of RA markers rheumatoid factor (RF), cyclic citrullinated peptide (CCP), anti-keratin antibody (AKA), and enzyme-linked immunosorbent assay method was used to determine the serum levels of inflammatory mediators high mobility group box 1 (HMGB1), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-6 (IL-6), interleukin-17 (IL-17) and interleukin-27 (IL-27).

2.5 Statistical methods

The specific values of tumor marker, RA marker and inflammatory mediator contents were input in SPSS 23.0 to obtain the statistic P after system calculation, and the differences were statistically significant if P<0.05 in the study.

3. Results

3.1 Tumor markers

Comparison of serum tumor markers CA199 (U/mL), CA153 (U/mL) and CEA (ng/mL) levels among the three groups was as follows: serum CA199, CA153 and CEA levels of combined disease group and RA group were higher than those of control group, and serum CA199, CA153 and CEA levels of combined disease group were higher than those of RA group. Differences in serum tumor markers CA199, CA153 and CEA levels were statistically significant among the three groups (P<0.05), shown in Table 1.

3.2 RA markers

Comparison of serum RA markers RF (IU/mL), CCP (IU/mL), AKA (IU/mL) and GPI (μg/mL) levels among the three groups was as follows: serum RF, CCP, AKA and GPI levels of combined
Severe cases may even cause respiratory failure and even death. Patients are characterized by mixed ventilation dysfunction, and combined with ILD mainly involves interstitial tissue and bronchiole, and such patients are difficult to treat and have poor prognosis. RA combined with ILD is one of the most serious complications of RA, and about 30% of patients may be combined with lung injury. RA is the most common autoimmune disease in clinical practice.

### 4. Discussion

RA is the most common autoimmune disease in clinical practice and about 30% of patients may be combined with lung injury. RA combined with ILD is one of the most serious complications of RA, and such patients are difficult to treat and have poor prognosis. RA combined with ILD mainly involves interstitial tissue and bronchiole, patients are characterized by mixed ventilation dysfunction, and severe cases may even cause respiratory failure and even death[5,6]. How to early identify patients with RA combined with ILD is the focus of clinical research at present. Lung biopsy is the gold standard to identify the existence of ILD, but it is invasive and is less adopted in clinical practice. Current studies have indicated that the contents of some tumor markers may fluctuate in patients with ILD, which may be used the effective indicators for early diagnosis of disease[7,8]. In this paper, serum levels of tumor markers were first compared among the healthy volunteers, patients with RA alone and patients with RA combined with ILD, and it was found that compared with those of normal control group, serum CA199, CA153 and CEA levels of RA group and combined disease group significantly increased, the increase of combined disease group was bigger, it means that there are significant changes in serum levels of tumor markers such as CA199, CA153 and CEA in patients with RA combined with ILD, and they can be used as the auxiliary indexes for disease diagnosis. The internal relationship between the above tumor marker levels and the disease severity in patients with RA combined with ILD will be elaborated below.

There are many specific indicators in the serum of RA patients, including RF, CCP, AKA, GPI, etc., which have been proven in a variety of studies to play an important role in disease diagnosis and illness assessment[9]. In addition to pulmonary manifestations, RA is more serious in RA patients with ILD, so the serum contents of above four markers can further change[10]. In this paper, the results showed that compared with those of normal control group, serum RF, CCP, AKA and GPI levels of RA group and combined disease group were higher, this is consistent with the RA condition, the increase of RF and GPI levels in combined disease group was more significant whereas CCP and AKA levels didn’t further increase, and it illustrates that the RF and GPI levels can be used as the sensitive indicators to determine whether RA patients are combined with ILD. Correlation analysis further showed that serum CA199, CA153 and CEA levels in patients with RA combined with ILD were positively correlated with RF and GPI levels, which explains that tumor marker levels can objectively reflect the autoimmune disease severity in patients with RA combined with ILD.

RA is essentially a chronic inflammatory disease, and the aggravation of inflammation is one of the core mechanisms causing the occurrence of ILD, so it is speculated that the levels of a variety of inflammatory mediators change in patients with RA combined with ILD, and they can be used as another effective indexes to measure the patients' condition[11]. HMGB1 is a new type of late inflammatory factor, it plays a significant role in pulmonary fibrosis, the content of HMGB1 increases significantly.

### Table 3.

Comparison of serum inflammatory mediator levels among the three groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>HMGB1 (ng/mL)</th>
<th>GM-CSF (pg/mL)</th>
<th>IL-6 (pg/mL)</th>
<th>IL-17 (pg/mL)</th>
<th>IL-27 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>5.18±0.63</td>
<td>11.04±1.61</td>
<td>20.47±2.85</td>
<td>7.43±0.95</td>
<td>18.34±2.18</td>
</tr>
<tr>
<td>RA group</td>
<td>47</td>
<td>13.29±1.65</td>
<td>23.77±3.09</td>
<td>32.64±4.81</td>
<td>15.48±1.79</td>
<td>40.21±5.84</td>
</tr>
<tr>
<td>Combined disease group</td>
<td>28</td>
<td>38.55±5.12</td>
<td>49.26±6.55</td>
<td>57.12±7.28</td>
<td>30.51±4.38</td>
<td>78.05±9.15</td>
</tr>
</tbody>
</table>

Note: compared with control group, $P<0.05$; compared with RA group, $P<0.05$.
especially when ILD occurs, and it participates in the occurrence and development of diseases[12]; GM-CSF is synthesized by endothelial cells, macrophages, activated T cells and so on, it is highly expressed in patients with active RA and can promote the secretion of IL-6 and other inflammatory cytokines and engulf pathogens, and studies have confirmed that GM-CSF antibody can alleviate animal autoimmune inflammation[13]; both IL-6 and IL-17 are the most typical inflammatory factors, which play a powerful pro-inflammatory role, and can induce the synthesis and secretion of other inflammatory factors and participate in the inflammatory cascade reaction[14]; IL-27 plays a dual immunomodulatory role and can promote the secretion of IL-10 and Treg cells and inhibit the production of Th17 cells, and studies have confirmed that serum IL-27 level in RA patients is obviously positively correlated with RA activity score[15]. The study results showed that compared with those of normal control group, serum HMGB1, GM-CSF, IL-6, IL-17 and IL-27 levels of RA group and combined disease group were higher. Correlation analysis further showed that serum CA199, CA153 and CEA levels in patients with RA combined with I LD were positively correlated with HMGB1, GM-CSF, IL-6, IL-17 and IL-27 levels, which confirms that tumor marker levels can objectively reflect the systemic inflammation in patients with RA combined with ILD.

Thus, it comes to the conclusion that serum tumor markers CA199, CA153 and CEA levels abnormally increase in patients with RA combined with ILD, the specific levels are positively correlated with the rheumatism condition and systemic inflammatory response degree, and they can be used as the reliable indexes to early screen for ILD in patients with RA and evaluate the disease severity in time.

References


