Anti CCP Antibodies in Tuberculosis

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Abstract

Introduction: Anti-cyclic citrullinated peptide (anti-CCP) antibodies have been considered very specific for rheumatoid arthritis (RA). Some studies have shown that these antibodies can be positive in infectious diseases like TB, HIV, etc.

Methods: Fifty patients of tuberculosis both pulmonary and extra-pulmonary were enrolled in the study from inpatient and outpatient departments from May 2012 to November 2013. Anti-CCP antibody test was done in all the patient by ELISA.

Results: Thirty one were pulmonary and 17 were extra-pulmonary and two were disseminated extra-pulmonary TB. Of the 31 cases of pulmonary tuberculosis, 12 cases (38.7%) were positive for anti-CCP antibodies and 19 cases (61.3%) were negative for same. Of the 19 cases of extra-pulmonary tuberculosis, two cases (10.52%) were positive for anti-CCP antibodies and 17 cases (89.48%) were negative. Of the 31 patients of pulmonary TB, nine were sputum positive and 22 were negative. Of those with sputum positive five (55.56%) were positive for anti-CCP antibodies and those with sputum negative 7 cases (31.81%) were positive for anti-CCP antibodies.

Conclusion: Anti-CCP can be falsely positive in cases of tuberculosis. Positivity of anti-CCP antibodies for tuberculosis is more for pulmonary (more for sputum-positive than sputum-negative) than extra-pulmonary TB. Anti-CCP thus is not very specific for rheumatoid arthritis.

Editorial Viewpoint

• Anti-CCP antibodies can be false-positive in infectious diseases.
• Anti-CCP antibody is not very specific for rheumatoid arthritis.
• Larger sample size and multi-centric studies should be done to assess its prevalence in various disease conditions.

Introduction

Anti-cyclic citrullinated peptide (anti-CCP) antibodies have been considered very specific for rheumatoid arthritis (RA). The introduction of tests recognizing anti-CCP has caused a revolution in rheumatology.¹,² The presence of antibodies against citrullinated proteins is a feature that was considered to be unique for rheumatoid arthritis. However, recently anti-CCP antibodies have been detected in patients suffering from infectious diseases like tuberculosis (TB), human immunodeficiency virus (HIV), leprosy, leishmaniasis and others.³ There is data reported from Japan, Israel and Brazil about anti-CCP positivity in tuberculosis. However, no data is available from India. Hence, this study was designed to corroborate the positivity of anti-CCP antibodies in tuberculosis because the prevalence of tuberculosis is very high in India. To the best of our knowledge, this is the first study from India evaluating anti-CCP antibodies in tuberculosis.

Material and Methods

This was a prospective observational study done at the B.Y.L. Nair Charitable Hospital in Mumbai, India. The study protocol was approved by the Institutional Ethics Committee of Nair Hospital. Fifty patients were enrolled in the study between May 2012 and November 2013. A written informed consent was taken from each patient. Patients suffering from pulmonary or extrapulmonary tuberculosis for the first time, that were drug naïve for ATT (anti-tuberculous treatment), were selected from inpatient wards and outpatient department of Nair hospital. The diagnosis of tuberculosis was made on the basis of clinical features, radiology, sputum smear examination for acid fast bacilli by Ziehl Neelson staining and culture, pleural fluid, cerebrospinal fluid reports and fine needle aspiration cytology of lymph-nodes demonstrating the histopathology of tuberculosis. Patients with HIV-TB co-infection and patients of inflammatory arthritis were excluded.

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Table 1: Total cases enrolled of extra-pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Type of extra-pulmonary tuberculosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal</td>
<td>3</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>3</td>
</tr>
<tr>
<td>Bone involvement</td>
<td>1</td>
</tr>
<tr>
<td>Choroid granuloma</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 2: Anti-CCP positivity in PTB

<table>
<thead>
<tr>
<th>Sputum</th>
<th>Cases of PTB</th>
<th>Anti-CCP +ve</th>
<th>Anti-CCP -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>31</td>
<td>12 (38.7)</td>
<td>19</td>
</tr>
<tr>
<td>Sputum positive</td>
<td>9</td>
<td>5 (55.6)</td>
<td>4</td>
</tr>
<tr>
<td>Sputum negative</td>
<td>22</td>
<td>7 (31.8)</td>
<td>15</td>
</tr>
</tbody>
</table>

All figures numbers (%)

Blood counts, liver and renal function tests, serum electrolytes erythrocyte sedimentation rate were done on each patient. Chest X-rays, pleural fluid analysis, ultrasound thorax and abdomen, CT scan of brain, thorax or abdomen, MRI brain, sputum for acid fast bacilli, fundoscopy, cerebrospinal fluid analysis and culture of Mycobacterium tuberculosis were done as per individual patient’s requirement for the diagnosis of tuberculosis. Anti-CCP antibody was tested by 2nd generation ELISA on each patient and results were obtained with specific titres. The titres of >14 IU/ml were considered positive as specified by the laboratory (0-14 IU/ml negative as per the laboratory range).

Results

Fifty patients of tuberculosis were enrolled in the study; of which 31 were diagnosed to have pulmonary TB, 17 were extra-pulmonary and two were disseminated extra-pulmonary TB. The distribution of the extra-pulmonary cases is shown in Table 1.

Pulmonary tuberculosis was subdivided based on sputum positivity for acid fast bacillus. Table 2 shows the distribution of pulmonary TB cases as regards anti-CCP antibodies. Of the 31 patients of pulmonary TB, nine were sputum positive and 22 were sputum negative. Of the nine sputum positive, five (55.56%) were positive for anti-CCP antibodies and four were negative. Out of 22 sputum negative, seven (31.81%) were positive for anti CCP antibodies. Thus anti-CCP positivity (in percentage) was more in sputum-positive than sputum-negative tuberculosis in this study. In total anti-CCP antibodies were positive in 12 cases (38.70%) of pulmonary tuberculosis and negative in nineteen (61.30%).

Table 3 shows the distribution of extra-pulmonary TB cases as regards anti-CCP antibodies. Due to a smaller sample size of individual extra-pulmonary TB cases, no concrete conclusions can be drawn. However, this is an eye-opener to conduct further research in this field.

Statistical analysis with Chi Square test was applied using SPSS software version 16 to compare the correlation between pulmonary and extra-pulmonary cases of tuberculosis and their anti-CCP values. There was a statistical significance while comparing the pulmonary and extra-pulmonary tuberculosis cases as regards to anti-CCP antibodies (p<0.05).

Discussion

The earlier studies done in several countries have documented anti-CCP antibody positivity in pulmonary tuberculosis. The first study was reported by Elkayam et al from Israel in 2006 in which 47 cases of pulmonary TB were tested for anti-CCP antibodies of which 15 cases (32%) were positive.

Second study was reported by Kakumanu et al from Japan in 2008 where 49 cases of pulmonary TB were enrolled and their anti-CCP antibody titers estimated. Kakumanu et al have reported 18 cases (37%) positivity for anti-CCP antibodies. In a recently published study by Lima et al from Brazil in 2013, only 2 (4%) of the 50 cases of pulmonary TB tested positive for anti CCP antibodies. Table 4 enumerates the various studies of anti-CCP positivity in tuberculosis.

In our study we compared anti-CCP antibodies in pulmonary as well as extra-pulmonary tuberculosis. Of the 31 cases of pulmonary TB, 12 (38.70%) were positive for anti-CCP antibodies. Thus our results were similar to the first two studies mentioned above. We also found that anti-CCP antibody was positive in two out of 19 cases of extra-pulmonary TB (10.5%). In patients with TB pleural effusion (n=7), CNS tuberculosis (n=3) and osteoarticular tuberculosis (n=3) none were positive for anti-CCP antibodies. Whereas one case of abdominal TB (n=3) (33.33%) and one case of TB choroid granuloma (n=1) (100%) were positive for anti-CCP antibodies. None of the two cases of disseminated extra-pulmonary TB were positive.
for anti-CCP antibodies. Thus it could be derived that anti-CCP antibodies may not be present in high titer in cases of CNS, bone involvement and disseminated tuberculosis as usually they have decreased immunity and thus may not mount higher titer of anti-CCP antibodies. Previous studies have not tested anti-CCP positivity in extra-pulmonary tuberculosis. This was an additional aspect of our study.

In this study three cases of pulmonary TB had hemoptysis of which all (i.e. 100%) were positive for anti-CCP antibodies. Also three cases had ATT-induced hepatitis of which two cases (i.e. 66.67%) were positive for anti-CCP antibodies. Due to these small numbers we cannot derive any significant conclusions from these three cases; however whether anti-CCP antibodies could be predictor of hemoptysis or drug-induced hepatitis in this situation is an unanswered question. A further study with a larger sample size is recommended to confirm these findings and to draw any reasonable conclusions.

The major limitation of our study was a small sample size due to financial constraints. However, after comparing the results with the earlier reported studies, our sample size and results are at par with the studies reported from Israel and Japan. It is recommended to conduct a further research in this field with a larger sample size recruiting equal number of pulmonary, extra-pulmonary cases and controls in 1:1:1 ratio to reproduce our results and answer the unanswered questions in this field.

Conclusions

Anti-CCP antibodies can be falsely positive in cases of tuberculosis. Positivity of anti-CCP antibodies for tuberculosis is more for pulmonary (more for sputum positive than sputum negative) than extra-pulmonary TB. The low prevalence of anti-CCP positivity in extrapulmonary tuberculosis could be due to decreased ability of patients to mount an inflammatory response in cases of disseminated tuberculosis and CNS tuberculosis. It is postulated that anti-CCP positivity in tuberculosis is secondary to citrullinated proteins in granulomas. Anti-CCP thus is not very specific for rheumatoid arthritis. Its positivity in other diseases like TB cannot be ignored, especially in a country like India where tuberculosis is highly prevalent.

References