Prevalence of antineutrophil cytoplasmic autoantibodies in patients with tuberculosis

L. F. Flores-Suárez¹, J. Cabiedes¹, A. R. Villa², F. J. van der Woude³ and J. Alcocer-Varela¹

Objective. To determine the prevalence of antineutrophil cytoplasmic autoantibodies (ANCA) in sera of patients with tuberculosis compared with healthy control subjects and a group of patients with atopic asthma.

Methods. The presence of ANCA was examined in patients with tuberculosis, and in asthmatic patients and healthy subjects as control groups, by means of indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA) to detect anti-proteinase 3 (PR3-ANCA) and antmyeloperoxidase (MPO-ANCA) antibodies.

Results. ANCA were present in 20 (44.4%) of 45 tuberculosis patients by IIF (16 c-ANCA, four p-ANCA) and in 18 (40%) patients by ELISA (15 PR3-ANCA, three MPO-ANCA). High odds ratios for ANCA positivity were observed for tuberculosis patients when compared with both control groups. ANCA results were not related to the category of tuberculosis, stage of disease, presence of concomitant diseases or pharmacotherapy.

Conclusions. As many clinical similarities between tuberculosis and Wegener’s granulomatosis exist, we propose that a positive ANCA test in patients living in countries with a high prevalence of tuberculosis must be carefully interpreted as indicative of systemic vasculitis, especially when no signs of extrapulmonary involvement occur.

Key words: Antineutrophil cytoplasm autoantibodies, Tuberculosis.
lungs of patients with WG are radiologically similar to the caseous necrosis seen in tuberculosis [2]. It is noteworthy that vasculitis has also been reported in tuberculosis patients [7].

ANCA directed against proteinase 3 (PR3) and myeloperoxidase (MPO) have been especially useful in the diagnosis of primary systemic vasculitides (PSV). They are reasonably sensitive and highly specific for small-vessel vasculitides, such as WG, microscopic polyangiitis and Churg–Strauss syndrome [8]. Nonetheless, ANCA detected by indirect immunofluorescence (IIF) have been observed in certain infectious diseases, such as onchocerciasis, leprosy, invasive amoebiasis, infective endocarditis, malaria, atypical pneumonias and respiratory tract infections, poststreptococcal glomerulonephritis, blastomycosis, chromomycosis and leptospirosis [9–20]. In most of these conditions, PR3 and MPO are not the main antigens targeted.

There have been previous case reports of ANCA in tuberculosis patients, mainly reported in abstract form and case reports [21], and also in a limited population of HIV-positive patients with pulmonary tuberculosis [22]. Because of the high prevalence of tuberculosis in Mexico, as well as the similarity in clinical and histopathological picture between tuberculosis and WG and Churg–Strauss syndrome, we undertook a study to measure the prevalence of ANCA in patients with tuberculosis. Our objective was to determine the prevalence of ANCA in sera of patients with tuberculosis compared with healthy control subjects and a group of patients with atopic asthma.

Material and methods

Disease definitions

Patients with tuberculosis. Patients with ‘definitive tuberculosis’ included those who, in addition to clinical and radiological signs and symptoms, had positive cultures for *M. tuberculosis*. Patients with ‘probable tuberculosis’ were those who had clinical–radiological manifestations of mycobacterial disease but also acid-fast bacilli under direct microscopic observation with Ziehl-Neelsen staining of sputum or other body fluids, and had a favourable response to antituberculosis treatment.

All patients came from the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) or the Instituto Nacional de Enfermedades Respiratorias (INER), both tertiary care referral centres in Mexico City. Most of them lived in the metropolitan area of Mexico City, although some of them came from locations outside it. These patients were studied between December 1994 and April 1995. All patients were in-patients with tuberculosis at either of the institutions, and most of the patients studied were consecutive. No patient with tuberculosis had signs or symptoms suggestive of a PSV and none was HIV-infected. Patients were categorized as active when there were clinical and/or radiological signs of disease activity. In some patients, categorization as treatment-resistant was based either on sensitivity results from cultures or on no response and/or persistent positive sputum smears in spite of treatment with isoniazid, rifampicin and pyrazinamide for the first month. This led to the introduction of other drugs in the therapeutic scheme, with favourable response in these cases.

Patients with atopic asthma. Sera from 47 asthmatic patients were analysed for the presence of ANCA. Sera from this patient population were obtained between June 1999 and June 2000 from the Hospital de Especialidades, Centro Médico La Raza, Instituto Mexicano del Seguro Social. At the time of sample collection, these patients had no other concomitant diseases. The choice of these patients as a control group was based on availability, partly similar pathogenic mechanisms and cytokine secretion profiles like those of WG and Churg–Strauss syndrome [23–26]. Also, there is one publication in which IIF-ANCA positivity occurred in 20% of a group of patients with atopic asthma [27].

Control subjects. Forty-seven healthy individuals were also tested for the presence of ANCA. None had been vaccinated for tuberculosis and none had a recent infection. All were either laboratory personnel or healthy blood donors attending the blood bank of the INCMSZ between December 1994 and April 1995.

ANCA testing

ANCA were tested for by IIF and two enzyme-linked immunosorbent assays (ELISAs). IIF was performed using commercially acquired slides with ethanol-fixed neutrophils (The Binding Site, Birmingham, UK) according to the manufacturer’s instructions. When a perinuclear ANCA (p-ANCA) pattern was found, the result was confirmed by the use of formaldehyde-fixed granulocytes. For this purpose, granulocytes were isolated from healthy donors using a Ficoll–Hypaque centrifugation gradient. Neutrophils were separated with a 5% dextran gradient. After the cells had been washed and pelleted, they were diluted to a concentration of 1 × 10^6 cells/ml, after which they were deposited on a 22% bovine albumin-coated slide by cytocentrifugation. After air-drying, cells were fixed for 5–10 min in 4% formaldehyde, air-dried again and then stored at −20°C until use. Sera to be tested were diluted 1:20. When a positive result was obtained, further dilutions were made until fluorescence was no longer detectable. Results are expressed as the maximal dilution observed. Antibodies against MPO and PR3 were detected with a commercially available ELISA assay (DLD Diagnostika, Hamburg, Germany) according to the manufacturer’s instructions. This assay uses direct coating of plates with either PR3 or MPO. PR3 isolation followed a method described previously [28]. No modifications of the procedure given by the manufacturer were introduced. All sera were tested, irrespective of the IIF result, and ANCA against PR3 and MPO were sought. For both antigens, we interpreted the results as follows: < 10 U/ml, negative; 10–20 U/ml, doubtful; > 20 U/ml, positive.

Statistical analysis

To measure the association between ANCA status and the probability of having tuberculosis, we used the odds ratio (OR). The statistical significance of our findings was tested by means of Pearson’s χ² test with Yates’ correction, and calculation of the 95% confidence intervals. Significance was established by a P value < 0.05.

Results

Demographic characteristics of the groups studied are shown in Table 1. The mean age of patients with atopic asthma was significantly lower in comparison with the other groups as it included children (P < 0.0001). No
ANCA in tuberculosis

Table 1. Demographic characteristics of the groups studied

<table>
<thead>
<tr>
<th></th>
<th>Patients with tuberculosis (n = 45)</th>
<th>Healthy subjects (n = 47)</th>
<th>Patients with atopic asthma (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>40.3 ± 15.5</td>
<td>37.2 ± 10.8</td>
<td>25.3 ± 15.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (46.6%)</td>
<td>15 (32%)</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>Male</td>
<td>24 (53.3%)</td>
<td>32 (68%)</td>
<td>24 (51%)</td>
</tr>
<tr>
<td>Category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitive</td>
<td>7 (15.5%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Probable</td>
<td>38 (84.5%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Stage of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>39 (86.6%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Inactive</td>
<td>6 (13.3%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>15 (33.3%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Absent</td>
<td>30 (66.7%)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

n.a. = not applicable.

Table 2. Drugs received by the patients with tuberculosis at time of serum sampling (numbers of patients)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with tuberculosis (n = 45)</th>
<th>Healthy subjects (n = 47)</th>
<th>Patients with atopic asthma (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;b&lt;/sup&gt;</td>
<td>35</td>
<td>Clofazimine</td>
<td>4</td>
</tr>
<tr>
<td>Rifampicin&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32</td>
<td>Roxithromycin</td>
<td>4</td>
</tr>
<tr>
<td>Pyrazinamide&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32</td>
<td>Clarithromycin</td>
<td>3</td>
</tr>
<tr>
<td>Ethambutol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12</td>
<td>Cefalosporin&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin</td>
<td>9</td>
<td>Kanamycin</td>
<td>1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>7</td>
<td>Prednisone&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>Protonamide</td>
<td>5</td>
<td>None&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>4</td>
<td></td>
<td></td>
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</tbody>
</table>

<sup>a</sup>Isoniazid was taken either alone or in combination with rifampicin and isoniazid. Mean drug intake ± s.d. and median plus range are given in the text.

<sup>b</sup>These drugs were taken in combination with isoniazid for the mean time and median (days) specified in the text.

<sup>g</sup>Ethambutol was part of the initial therapeutic scheme (first 2–4 weeks) in combination with the usual drugs in 12 patients.

<sup>e</sup>Patient was receiving a second-generation cephalosporin because of concomitant acute bacterial bronchitis.

<sup>f</sup>The patient took prednisone because of long-lasting chronic asthma.

<sup>g</sup>All patients were inactive at the time of serum sampling.

pyrazinamide) at the time of analysis and blood sampling for ANCA. All these patients were seen during the first month after the diagnosis of pulmonary tuberculosis had been established. Length of treatment varied from 0 days to 1 month before serum was obtained for ANCA testing. The drug most widely taken before ANCA testing was isoniazid, with a mean time of intake of 7.7 ± 4.7 days (median 6, range 0–30), either alone (three cases) or in full combination with rifampicin and pyrazinamide, the mean time of intake of this combination being 7.7 ± 7.7 days (median 6, range 0–30). Twelve of the 39 active patients also received, as part of their initial drug regimen, ethambutol during the first weeks of treatment. There were nine resistant cases; these patients received the other drugs mentioned in Table 2.

One-third of the tuberculosis patients had concomitant diseases: eight had non-insulin-dependent diabetes mellitus, four had chronic cor pulmonale (one due to chronic asthma), three had giardiasis, and there was one case of each of the following: chronic alcoholic hepatopathy, bronchiectasias, acute bacterial bronchitis, chronic renal insufficiency of unknown cause (nondialysis-dependent), ascaridiasis, and intestinal non-invasive amoebiasis. Some had more than one of these diseases.

Of the healthy controls, two individuals had a positive IIF result, both showing p-ANCA at dilutions of 1:40 and 1:80 respectively, but none of them had a positive ELISA result. In the group of asthmatic controls, seven subjects showed a positive IIF reaction, with a perinuclear pattern, all with dilutions equal to 1:20, while three other subjects had a cytoplasmic staining pattern at the same dilution. Just one subject from this group had a positive MPO-ANCA result by ELISA (27 U/ml); this subject had a fine granular c-ANCA pattern on IIF.

As shown in Fig. 1A, 16 tuberculosis patients had a coarse granular c-ANCA-positive pattern by IIF and four were p-ANCA-positive (44.4% overall); 25 (55.6%) patients were IIF-negative. We observed no atypical ANCA patterns. Among the patients positive for IIF, 10 of the 16 with c-ANCA were positive at a dilution equal to or higher than 1:40, and two of those with p-ANCA were positive at a dilution equal to or higher than 1:40 (Fig. 1B). The highest observed dilutions were 1:320, both for c-ANCA (Fig. 1A). Regarding the ELISA results (Fig. 2), all except one in each group of IIF-positive patients showed a positive result against PR3 or MPO, 15 of the 16 c-ANCA who were positive by IIF showing PR3-ANCA and three of the four who had p-ANCA showing MPO-ANCA. Forty per cent of all tuberculosis patients were found to be positive by ELISA. No patient was positive for ELISA without also being positive in IIF, and no c-ANCA-positive patients were MPO-ANCA-positive as there were no p-ANCA positive patients with a positive PR3-ANCA result by ELISA. The actual values obtained in the solid-phase assays are shown in Fig. 2. In general terms, a direct correlation was observed between the levels seen in IIF and the values obtained with ELISA.

differences regarding sex distribution and age existed between the patients with tuberculosis and the healthy subjects. Forty-three patients had pulmonary tuberculosis, one had tuberculous empyema and one a tuberculous abscess in the psoas muscle. These two extrapulmonary patients had negative ANCA results by both methods used.

Table 2 shows the number of patients taking drugs for treatment of tuberculosis. Of the six inactive patients, five did not receive any treatment at the time of serum sampling and one was inactive after 5 months of therapy, close to completing the therapeutic scheme. Of the 39 active patients, four did not come back after discharge and no data on drug intake were available. Three additional patients had not taken rifampicin and pyrazinamide properly on a daily basis and they were omitted from the analysis of patients under these drugs. Therefore, thirty-five patients were taking isoniazid and 32 the full combination (isoniazid, rifampicin and
Comparisons between groups regarding ANCA positivity and the probability of having tuberculosis, expressed as the odds ratio with the 95% confidence interval, are shown in Table 3. These results are shown for each of the methods used to detect ANCA (IIF and ELISA). When we tested for associations between ANCA results and gender, age, presence of other concomitant diseases, type of disease (definitive or probable), stage of disease (active or inactive), disease localization, length of treatment and type of drugs received (a reflection of resistance), no correlation was observed with the data obtained.

A small group of tuberculosis patients from the original sample population (n = 18) could be tested again for ANCA, on average 3 yr after tuberculosis was diagnosed and treated, five of them being previously positive for ANCA by both IIF and ELISA. Of these, only one still proved to be positive for c-ANCA at 1:20 dilution, and ELISA of 22 U for PR3-ANCA. Another patient, previously c-ANCA-positive at 1:160 dilution with a positive ELISA of 29 U, tested positive for antinuclear antibodies with a coarse speckled pattern at 1:80 dilution and also a cytoplasmic pattern at the same dilution. This time his ANCA test was negative. The remaining patients, who were ANCA-negative at initial testing, remained so. However, two of the sera were positive for antinuclear antibodies at that time, one with a homogeneous pattern (negative for anti-Sm and Crithidia luciliae, apparently clinically asymptomatic) at a 1:640 dilution, and the other with a fine speckled pattern at a 1:5120 dilution (also apparently asymptomatic, and negative for anti-Sm and C. luciliae). At the time of serum sampling on that occasion, these two patients had not recently taken any antituberculous agents. No data about any other drugs being taken by these subjects at that time were recorded.

Fig. 1. (A) Maximal positive dilutions of c-ANCA as measured by IIF in ethanol-fixed neutrophils. There were 16 c-ANCA-positive tuberculosis patients, constituting 36% of the subjects in the group with tuberculosis, with titres ranging from 1:20 (six subjects) to 1:320 (two subjects). The tuberculosis patients shown here as negative (25 subjects, 55%) were also negative for p-ANCA. There were three positive c-ANCA individuals within the group of asthmatic patients, all with a titre of 1:20. None was positive for either PR3 or MPO-ANCA in ELISA. None of the healthy control subjects was positive for c-ANCA. (B) Maximal positive dilutions of p-ANCA as measured by IIF in ethanol-fixed neutrophils. In all cases, p-ANCA-positive patients had cytoplasmic staining when formalin-fixed neutrophils were used. The group of tuberculosis patients included four p-ANCA-positive subjects (9% of all tuberculosis patients) with dilutions ranging from 1:20 (two individuals) to 1:160 (one individual). The tuberculosis patients shown here as negative (25 subjects, 55%) were also negative for c-ANCA. Seven asthmatic patients had positive p-ANCA results, all at 1:20 dilution, one also being positive for MPO-ANCA (see text and Fig. 2). Two of the healthy controls were also positive for p-ANCA, at titres of 1:40 and 1:80 respectively, although none was positive in ELISA for either PR3 or MPO-ANCA.

Fig. 2. ELISA results for both main antigens detected by ANCA testing in the group of patients with tuberculosis. Fifteen of 16 c-ANCA-positive patients had a positive result for PR3 ANCA, and three-quarters of the p-ANCA-positive patients were positive for MPO-ANCA. For both tests, a value above 20 U/ml was taken to be a positive result (dotted line). Mean values are depicted by the short lines (51.2 U/ml for PR3-ANCA-positive tuberculosis patients, 60.4 U/ml for MPO-ANCA-positive tuberculosis patients). All anti-MPO-positive patients had levels higher than 40 U. One of the 47 asthmatic patients, who was p-ANCA-positive, was positive for MPO-ANCA (27 U/ml, not shown). No healthy control had a positive ELISA result for either antigen tested.
TABLE 3. Association between ANCA positivity and the probability of tuberculosis expressed as the odds ratio (OR) with 95% confidence interval (CI).

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA by IIF (positive for c- or p-ANCA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis vs healthy subjects</td>
<td>18</td>
<td>3.88–83.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Tuberculosis vs asthmatic subjects</td>
<td>2.96</td>
<td>1.19–7.38</td>
<td>&lt; 0.027</td>
</tr>
<tr>
<td>ANCA by ELISA (positive for PR3-ANCA or MPO-ANCA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis vs healthy subjects</td>
<td>63.9</td>
<td>8.6–∞</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Tuberculosis vs asthmatic subjects</td>
<td>30.7</td>
<td>3.87–243</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Discussion

There have been conflicting results regarding the presence of ANCA in tuberculosis. Dannenberg et al. [29] studied 50 patients in Germany and found no ANCA in this group except for one said to be positive for MPO-ANCA. However, it seems that some patients from Germany and with proven, culture-positive tuberculosis, develop ANCA with specificity against bactericidal/permeability-increasing protein (BPI) (E. Csernok, personal communication). We are to begin a study of BPI-ANCA in newly diagnosed patients with tuberculosis, in which we intend to extend and confirm the observations presented here and study further the antigen–antibody reaction by means of more specific techniques (immunoblotting), which were not used in the present study. In previous studies dealing with ANCA in tuberculosis, positive ANCA results, as measured by IIF, were found in a subset of HIV-infected patients with pulmonary tuberculosis but not in those not infected with HIV or in pulmonary asymptomatic HIV-positive individuals [22].

There have been other mycobacterial diseases in which ANCA have been found. In a study in Mexico, Medina et al. [10] found ANCA positivity, as measured by IIF, in 10/38 lepromatous leprosy patients and in 1/6 with borderline leprosy, while ANCA were not found in patients with tuberculoid leprosy. Most of the patients were p-ANCA-positive, and some of the levels were as high as in our study. Interestingly, the two patients with the highest levels both had Lucio’s phenomenon (generalized necrotizing vasculitis and fever in the context of leprosy). It is worth mentioning that the authors did not find any correlation with activity parameters of disease, as was the case in our study. This was also the case for the findings of a study performed in Brazil, where ANCA positivity in leprosy patients was found, though the pattern observed by IIF was atypical. In this study, no IIF-positive patients showed antibodies against the two major ANCA antigens by ELISA [11]. Results in patients with chromomycosis were similar to those seen in leprosy, 20% of patients being positive with a cytoplasmic IIF pattern, and by ELISA all showed a reaction against antigens present in a primary neutrophil granule extract, though not with isolated PR3. With regard to clinical parameters, more dermal lesions were found in ANCA-positive than in ANCA-negative patients [19].

There have been positive ANCA results in case reports of patients with tuberculosis [21]. Most of them showed a c-ANCA pattern, in some cases leading to a diagnosis of WG. However, at the time of these reports, ELISAs for antigen specificities were not performed. We decided to undertake the present study in a sample of patients with tuberculosis as the prevalence of this disease in Mexico is high. One drawback of our study is that many of the patients did not have a positive culture for *M. tuberculosis*, though the clinical and radiological characteristics with positive sputum smears for bacilli and the subsequent response to treatment proved to be compatible with this diagnosis. Some patients could be followed for up to 3 yr after the diagnosis of tuberculosis had been made, and until then none had developed signs of PSV. However, this was a small group, and many of them returned to their community health centres and have not been referred to us again. Therefore, we have not been able to follow the majority of these patients longitudinally.

Though it might be reasonable to explain positive IIF results as being false positive because of the low levels seen (1:20) in 8/20 sera, our results are surprising in terms of ELISA. We cannot give a satisfactory explanation for this. However, the ANCA results in our patients are comparable to those found in lepromatous leprosy patients [11], in which other autoantibodies have also been shown. Both diseases (lepromatous leprosy and active tuberculosis) share the characteristic of high mycobacterial counts in affected tissues, as opposed to what is seen in the other pole of lepromatous disease, tuberculoid leprosy. Besides, the majority of our tuberculosis patients were bacilliphilic and active at the time of ANCA testing. Although the IIF pattern observed in our c-ANCA-positive tuberculosis patients was coarse granular, as opposed to the fine granular pattern observed when BPI is the antigen recognized, and in 15/16 of the c-ANCA-positive patients the ELISA recognized PR3 as antigen, there is a possibility that BPI could also account for the immunofluorescence observed, as BPI-ANCA have been observed in the context of chronic, long-standing infections, as in the case of cystic fibrosis [30, 31]. We did not test for BPI-ANCA, but a study with newly diagnosed tuberculosis patients is being launched.

It has recently been shown that *M. tuberculosis* can stimulate the release of oxygen metabolites from neutrophils that are activated through interaction with the phenol glycolipids of the cell wall of *M. tuberculosis* [5]. This activation most likely leads to the release of lysosomal enzymes from the neutrophils in the initial stages of the mycobacterial infection, and autoantibodies against the granular components of those cells can develop.

Another plausible explanation for the production of ANCA in these patients is the therapy received. It is well known that some drugs, especially isoniazid in the present disease context, can be transformed by MPO into active metabolites with the development of cytotoxic products [32]. Presumably, cytotoxicity could...
generate neutrophil damage with, in theory, subsequent synthesis of PR3 and MPO-ANCA, which would explain the observed presence of anti-MPO autoantibodies in some subjects taking drugs like isoniazid, among others described previously [32, 33]. Though all MPO-ANCA-positive patients received isoniazid, we did not find a correlation between drug intake and the presence of ANCA, and patients had not received treatment for more than 30 days when ANCA testing was performed. Additionally most patients reacted against PR3, four of the 15 PR3-ANCA-positive patients not taking isoniazid at the time of serum testing. No relationship was found between any of the drugs patients were taking and the ANCA test results.

Tuberculosis and WG share some clinical, histopathological, immunological and even pathogenetic features. The release of cytokines and chemokines plays a fundamental role in both diseases and in the development of granulomas, a characteristic feature of tuberculosis. Finding granulomas may support a diagnosis of WG in the adequate clinical context, although it is not a frequent feature [24, 34–37]. Both pulmonary and extrapulmonary vasculitis has been reported in tuberculosis [38] and, as stated by Gordon et al. [7], histopathological findings in both entities could reflect similar pathogenetic mechanisms.

The consequences of assuming that a positive ANCA result is due to WG without a thorough investigation of tuberculosis, especially in countries with a high prevalence of that disease, in subjects from groups with a high risk of contracting M. tuberculosis infection or subjects in whom reactivation may happen, cannot be overemphasized, in particular with respect to therapeutic decisions. Under these conditions, we advise against the straightforward interpretation of an ANCA-positive result as indicative of PSV, especially WG, most importantly when there are no extrapulmonary manifestations of such diseases.

Acknowledgements

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