Thrombocytosis Is Associated With *Mycobacterium tuberculosis* Infection and Positive Acid-Fast Stains in Granulomas

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**Key Words:** Mycobacteria; Tuberculosis; Thrombocytosis; Acid-fast stain; Granuloma

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**Abstract**

*Mycobacterium tuberculosis* infection is associated with thrombocytosis. We sought to determine if this information might be valuable in evaluating granulomas using acid-fast stains (AFS). Fifty-eight patients with culture-confirmed *M tuberculosis* infection were compared with 75 patients with atypical mycobacterial infection and 48 patients negative for mycobacteria. Thrombocytosis (platelet count >360 × 10^3 μL [360 × 10^9/L]) was significantly more common in patients with *M tuberculosis* (50%) than those with either atypical mycobacterial infection (12%) or negative for mycobacteria (4%, *P* < .001 for each). In 67 patients, histologic evaluation of tissue samples showed granulomatous inflammation; 37 (55%) had positive AFS results. Of 19 patients with thrombocytosis, 16 (84%) had a positive AFS result compared with 21 (44%) of 48 without thrombocytosis (*P* = .003). Fifteen of 16 *M tuberculosis* cases with thrombocytosis had positive AFS findings on histologic evaluation; the single negative case had a platelet count of 362 × 10^3/μL (362 × 10^9/L). However, 3 of these cases of positive results on staining were initially diagnosed as negative and only recognized as positive on review. We conclude that patients whose specimens were sent for mycobacterial culture and thrombocytosis had an increased risk for *M tuberculosis*. Patients with granulomas and thrombocytosis are more likely to have a positive AFS result usually showing *M tuberculosis*. Finally, patients with initially negative AFS results and thrombocytosis deserve to have additional evaluation of the AFS specimens.

*Mycobacterium tuberculosis* infection is associated with thrombocytosis.1-11 This effect might be related to increased levels of interleukin 612 and may lead to a hypercoagulable state and deep vein thrombosis.8 The degree of thrombocytosis correlates significantly with the degree of inflammation as measured with the erythrocyte sedimentation rate and serum C-reactive protein.10 We sought to determine whether this information might be valuable in evaluating granulomas using acid-fast stains (AFS).

**Materials and Methods**

Patients who had undergone cultures for mycobacteria at Baptist Hospital (Miami, FL) were identified. All positive cultures from 2006 to 2011 were identified, as well as a consecutive series of negative cultures from September 2011 through December 2012. For each patient, the admitting platelet count (either on the day of admission or within 24 hours if not done on admission) was identified, as well as any material that was available for tissue diagnosis. Patients without an admitting platelet count were excluded; only 3 patients were excluded on this basis. Data on C-reactive protein, sedimentation rate, and D-dimer testing were also obtained from the admission medical records. All biopsy and AFS findings were reviewed. “Rare” organisms were defined as 2 or fewer organisms identified per slide.

Statistical analysis was performed with a 2-tailed Mann-Whitney *U* test for continuous data and a 2-tailed χ^2 test for categorical data. A *P* value of less than .05 was considered significant.
Results

Fifty-eight patients with culture-confirmed *M tuberculosis* infection were compared with 75 patients with atypical mycobacterial infection and 48 patients negative for mycobacteria. Atypical mycobacteria included 33 *Mycobacterium avium intracellulare*, 9 *Mycobacterium abscessus*, 1 *Mycobacterium asiaticum*, 1 *Mycobacterium chelonae*, 11 *Mycobacterium fortuitum*, 7 *Mycobacterium gordonae*, 6 *Mycobacterium kansasii*, 1 *Mycobacterium marinum*, and 6 nontuberculosis not otherwise specified (based on genetic testing).

Platelet counts are summarized in Table 1. Thrombocytosis (platelet count >360 × 10^3/μL [360 × 10^9/L]) was significantly more common in patients with *M tuberculosis* (50%) than either atypical mycobacterial infection (12%) or negative for mycobacteria (4%; *P* < .001 for each). Patients with known thrombocytosis and concurrent mycobacterial cultures were significantly more likely to have *M tuberculosis* (73%) than patients without thrombocytosis (20%; *P* < .001).

Histologic evaluation of tissue samples of 67 patients showed granulomatous inflammation Table 2. Of these, 31 had positive *M tuberculosis* cultures, 22 had positive atypical mycobacterial cultures, and 14 had negative cultures. AFS results were positive in 37 (55%) patients. Of 19 patients with thrombocytosis, 16 (84%) had a positive AFS result compared with 21 (44%) of 48 without thrombocytosis (*P* = .003). Of 16 *M tuberculosis* cases with thrombocytosis, 15 had positive AFS results on histologic evaluation, and the single negative case had a platelet count of 362 × 10^3/μL (362 × 10^9/L). However, 3 of these positive stains were initially diagnosed as negative and only recognized as positive on review.

Of the 21 positive AFS results in patients without thrombocytosis, 6 were identified as *M tuberculosis*, 12 were atypical mycobacterial, and 3 had negative cultures. In 2 of 6 cases of tuberculosis, platelet counts increased significantly within 48 hours of admission to 487 × 10^3/μL (487 × 10^9/L) and 510 × 10^3/μL (510 × 10^9/L). All 6 *M tuberculosis* cases had rare organisms. The 12 atypical mycobacterial cases had rare (*n* = 7) or abundant (*n* = 5) organisms. All cases with negative cultures and positive AFS had rare organisms.

Of 181 patients in this study, C-reactive protein levels were available in 2, sedimentation rate in 4, and D-dimer studies in 1. Because of these insufficient numbers, no further analysis was performed on these data.

Discussion

One of the more tedious tasks in histology is review of AFS specimens. When faced with a granuloma and an apparently negative AFS result, one is often stuck trying to decide how much longer to examine the AFS specimen and whether one should order additional staining. The advice that one of us (A.A.R.) received in residency from Janina Longtine, MD (who found far more acid-fast organisms than any other attending physician at that institution), was to look long enough to make sure that no one else would find an organism you missed; this is accurate, but not particularly helpful. As a result, any additional information that might help the pathologist decide on which granulomas to spend additional time would be helpful. We believe that the data we present herein are exactly that information.

The information is neither perfect nor complete. Both atypical mycobacterial and *M tuberculosis* cases do occur in patients without thrombocytosis, and in some cases, the AFS results are positive. Review of AFS results in patients without thrombocytosis remains a difficult task in which the expected outcome is not clear. Review of AFS can be aided by clinical information as well as histologic appearance in these cases. However, the expected outcome for review of AFS specimens in patients with granulomas and thrombocytosis is not unknown; one should expect to find acid-fast organisms in this setting. If the initial review of the AFS specimen in such

<table>
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<tr>
<th>Culture Result</th>
<th>No. of Patients</th>
<th>Granulomatous Inflammation on Biopsy</th>
<th>+ AFS</th>
<th>− AFS</th>
<th>+ AFS and Thrombocytosis</th>
<th>+ AFS and No Thrombocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>58</td>
<td>31</td>
<td>21</td>
<td>10</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>AM</td>
<td>75</td>
<td>22</td>
<td>13</td>
<td>9</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Negative</td>
<td>48</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>67</td>
<td>37</td>
<td>30</td>
<td>16</td>
<td>21</td>
</tr>
</tbody>
</table>

AFS, acid-fast stain; AM, atypical mycobacteria.
a setting is negative, the smear should be reviewed again or additional stains obtained. Nevertheless, the platelet count should be viewed as an additional piece of information to be used along with the histologic appearance and additional clinical information. The current study used the admission platelet count to allow uniform collection of data. However, in some cases the platelet count may increase after admission, and this may be a clue that pathologists can use to increase their suspicion of an *M tuberculosis* infection.

The degree of thrombocytosis is also associated with markers of inflammation (erythrocyte sedimentation rate and C-reactive protein). These markers may be valuable in determining how hard to examine an AFS specimen. Nevertheless, we were unable to analyze these variables because, unlike the platelet count, they were unavailable for most patients. At present, it is unclear whether they add value to the platelet count.

The value of platelet counts may depend on the patient population that is evaluated. Not all patients with *M tuberculosis* infection have thrombocytosis. Indeed, some patients present with low platelets, particularly in Third World settings. We hypothesize that thrombocytosis may be most useful in making a diagnosis in the industrialized world, where the stage of disease may not be as advanced and the underlying health of the patient may not be as poor as in other settings. Nevertheless, evaluation of these findings in other settings may be valuable.

We conclude that patients whose specimens were sent for mycobacterial culture and thrombocytosis evaluation had an increased risk for *M tuberculosis*. Patients with granulomas and thrombocytosis are more likely to have positive AFS results, which usually show *M tuberculosis*. Finally, patients with initially negative AFS results and thrombocytosis deserve to receive additional evaluation of the AFS.

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References