The Blood Counts and Lactate Dehydrogenase Levels in Thrombotic Thrombocytopenic Purpura (TTP)

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The blood counts and lactic dehydrogenase values of eight patients with thrombotic thrombocytopenic purpura (TTP) were reviewed in relation to the clinical course. Three of the eight patients died. In these patients, the hemoglobin was significantly lower and the LDH higher at the time of presentation than that of the patients responding to treatment. The height of the absolute reticulocyte count and platelet count did not correlate as well with outcome as did the degree of anemia and LDH elevation. Microangiopathic changes were noted in all eight patients. A differential count showed that the total microangiopathic changes varied from 0.8 to 54%. The more severe microangiopathic changes occurred in the fatal cases. The observations indicate that the degree of anemia, elevation of LDH, and severity of microangiopathic changes at the time of presentation correlate with the outcome in TTP and provide useful parameters in the assessment of response to therapy. (Key words: Thrombocytopenia; Anemia; Hemolysis; Microangiopathy; LDH) Am J Clin Pathol 1983; 80: 700-702

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) is an often lethal disorder characterized by hemolytic anemia with a microangiopathic blood picture, thrombocytopenia, fluctuating neurologic abnormalities, renal dysfunction, and fever. Pathologically, numerous microthrombi are evident in the skin, heart, kidneys, lungs, and brain. The etiology of this disorder is unknown, but some clinical observations have suggested that an infectious etiology as well as genetic factors may be important determinants of susceptibility. In addition to treatment with corticosteroids, recent therapeutic approaches employing plasma and plasma exchange have improved the outlook considerably. The variable clinical picture at presentation has made it difficult to evaluate the potential severity of the condition in a given patient. Eight patients with this problem have been seen at our institution in the past three years, and these cases provided an opportunity to correlate the clinical course and response to treatment of these patients with the conventional hematologic laboratory parameters obtained at the time of presentation. Some, but not all, abnormal laboratory measurements correlate with the eventual response to therapy.

Methods

Between September 1979 and January 1983, eight patients with TTP were diagnosed and treated. The diagnosis of TTP was based on abnormal neurologic and renal findings as well as the presence of hemolysis and thrombocytopenia in each patient. In seven of the eight patients there was no evidence of disseminated intravascular coagulation (DIC) by procoagulant or fibrin degradation products (FDP) assay, although in a single patient there was a modest increase in FDPs. The diagnosis was confirmed pathologically at autopsy in three, by skin biopsy in two, and splenectomy in one. In two patients the skin biopsy was equivocal. The patients were treated with a combination of corticosteroids, antiplatelet agents, and plasma as previously described. The red blood count, hemoglobin level, hematocrit, and red blood cell indexes were performed on a Coulter model S plus. The absolute reticulocyte count was calculated by multiplying the percentage of reticulocytes by supravital methylene blue staining by the red blood cell count. When an abnormal red blood cell size distribution was present, excess microcytes were counted as platelets and, when this occurred, the platelet counts were done on a Clay-Adams Ultra Flo 100 or by phase contrast microscopy. LDH was measured by monitoring the conversion of pyruvate to lactate at 340 nm in a Gilford spectrophotometer. LDH isoenzyme electrophoretic fractionation was performed in agarose at pH 8.6. The NADH reaction product was measured with a Corning 720 fluorometric spectrophotometer. Statistical analysis for the significance of differences between means was by the Student's unpaired t-test.

Results

Of the eight patients, three died and five survived. There was no significant correlation between the absolute re-
ticulocyte count or leukocyte count at the time of presentation and the outcome (Fig. 1). However the hemoglobin level did correlate significantly ($P < 0.05$) with outcome: 8.4 gm/dL in the nonfatal cases versus 5.4 gm/dL in the fatal cases. Lactic dehydrogenase levels (LDH) also were higher in the fatal than nonfatal cases. LDH fractionation was performed in four patients at a time when their LDH was above 1,000 IU/L. In these patients, 75% or more of the LDH was contained in fractions 1, 2, and 3, but all fractions were elevated.

Although the platelet count did not correlate significantly, it was higher in the nonfatal cases (Fig. 1). Moreover, in seven of eight patients responding clinically with improvement (clearance of neurologic findings, diminished purpura) the platelet count rose. There was a reciprocal relationship between LDH level that was seen initially and during fluctuations in the course of the disease (Fig. 2).

**Discussion**

Previous studies have indicated that there is a variation in hematologic abnormalities in TTP with no obvious relation to outcome. However, the information relating to blood counts often has been incomplete and previously has not been a subject of detailed analysis. Moreover, in most of the previous series, there was a very high fatality rate, often exceeding 80%. Thus, there was little likelihood that hematologic parameters at the time of presentation would have value in predicting the clinical course or prognosis, since most of the patients did not survive. In the present study, the degree of hemolytic anemia, as reflected in the hemoglobin concentration and the LDH levels, correlated well with the severity of the process and the response to therapy. The absence of correlation of the absolute reticulocyte count (Fig. 1) suggested that there may be a variation in marrow response to the disease. Since an infectious etiology has been suggested for this condition, a depression of the response of the marrow to the hemolytic anemia might be on that basis. The platelet count, which is believed to be primarily a result of depressed survival, might also reflect a partial depression in marrow production. Variation in the level of platelet counts for a given degree of hemolysis also might be based on individual variation in the susceptibility of the platelets to damage on the microthrombi or, more likely, subsequent removal of damaged or activated platelets in the spleen or liver.

There was a significant correlation between the initial serum LDH and the outcome, and increased LDH appeared to be primarily from the red blood cells, because it was contained in the first three fractions. The possibility that some of the LDH was released by the platelets or by microinfarcts also exists. The extensive nature of the thrombotic lesions throughout the myocardium, brain, and kidneys, which are all rich sources of LDH, would preclude a definitive attribution of the entire increase to hemolytic anemia. Nevertheless, the prompt and sustained fall in LDH that was seen in some patients (Fig. 2) and that often accompanied or preceded a rise in platelets, and improvement in clinical status, suggested that the LDH was correlated directly with disease activity. It has previously been well documented that significant fluctuations in LDH activity are indicative of a continued need for exchange plasmapheresis. We found the LDH to begin to improve coincidently with, or prior to, the rise in platelet count in each patient who responded to therapy.

**Table 1. The Percentage of Microangiopathic Red Blood Cells at the Time of Presentation in Patients with TTP**

<table>
<thead>
<tr>
<th>Red Blood Cells</th>
<th>Fragments</th>
<th>Spherocytes</th>
<th>Helmets</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fatalities</td>
<td>12.9 ± 5.6*</td>
<td>12.5 ± 8.2</td>
<td>1.7 ± 0.5</td>
<td>27.0 ± 14</td>
</tr>
<tr>
<td>2. Survivors</td>
<td>3.7 ± 1.5</td>
<td>3.5 ± 1.3</td>
<td>2.5 ± 0.8</td>
<td>9.7 ± 3.2</td>
</tr>
<tr>
<td>Total group</td>
<td>7.6 ± 2.9</td>
<td>7.4 ± 3.7</td>
<td>2.1 ± 0.5</td>
<td>17.1 ± 6.6</td>
</tr>
<tr>
<td>Range</td>
<td>0.3–23</td>
<td>0.1–29</td>
<td>0.4–3.7</td>
<td>0.8–53.8</td>
</tr>
</tbody>
</table>

* Mean ± SEM.
Microangiopathic changes were present in all patients (Table 1). Classic spherocytes and helmet forms were observed less frequently than deformed and irregularly fragmented red blood cells. The degree of microangiopathic changes, however, varied remarkably. There was a large absolute difference in the number of fragmented forms between patients who died and those who survived but, because of the variation, this large difference was not statistically significant. The manifestation of microangiopathic hemolysis would seem to depend not only on the number of microthrombi present but also on the clearance of fragmented red blood cells by the spleen. Patients who demonstrate very large numbers of microangiopathic changes may have exceeded the capacity of the spleen to remove these cells. The appearance of many Howell-Jolly bodies in one of the patients who died supports the concept that splenic clearance may be impaired in the fulminant phase of this disorder. Indeed, the prompt improvement in peripheral blood smear observed in some patients after plasma exchange suggests that improved splenic clearance of damaged red blood cells may be a major factor limiting further intravascular hemolysis.

References