A Study of Thrombocytopenia

New Histologic Criteria for the Differentiation of Idiopathic Thrombocytopenia and Thrombocytopenia Associated with Disseminated Lupus Erythematosus

By ROBERT T. BRECKENRIDGE, RICHARD D. MOORE AND OSCAR D. RATNOFF

THE SYMPTOMATOLOGY and course of the thrombocytopenic state which occurs in some patients with disseminated lupus erythematosus (DLE) closely mimics that of so-called idiopathic thrombocytopenic purpura (ITP).\textsuperscript{1-8} Because of these similarities, it has been suggested that ITP must be thought of as a syndrome rather than a disease entity, since this condition may arise from a variety of causes.\textsuperscript{10,11} There is, however, a significant number of patients in whom DLE is not clinically manifest, and no other overt cause for the thrombocytopenia can be discovered. These patients, tentatively, may be said to have ITP.

This study is an attempt to define criteria to distinguish between the purpuric states associated with DLE and those which may be classified, at least for the present, as ITP. A review of the records of patients studied at University Hospitals of Cleveland suggests that, if DLE is present, the diagnosis can usually be deduced either from the clinical data available at the time of splenectomy or from cellular alterations present in the excised spleen. The clinical course of the thrombocytopenic state in the two groups of patients does not appear to differ significantly.

MATERIALS AND METHODS

The records of all cases of thrombocytopenia in which splenectomy had been performed at University Hospitals of Cleveland from 1940 to 1965 were reviewed independently by two of us. In each case a judgment was made concerning an appropriate clinical diagnosis, both at the time of splenectomy and during the subsequent course of the patient's illness. In the few instances in which there was disagreement, a consensus was reached without knowledge of the pathologic findings.

Most of the patients whose records were reviewed had been seen by hematologists still on the staff of University Hospitals. It was therefore possible to determine their current condition in most cases. For the purposes of this study, a permanent remission of the
thrombocytopenia was defined as an initial rise in platelet count after splenectomy to $>300,000$ per mm.$^3$ and a level of $>150,000$ per mm.$^3$ thereafter without resort to therapy with steroids. A response to treatment with steroids was defined as a rise in the platelet count to $>120,000$ per mm.$^3$ and a cessation of the clinical bleeding. From the design of this study, however, no patient was included in whom there was a permanent remission following steroid therapy alone, since all patients included in our series had had a splenectomy.

The histologic sections of the spleens were reviewed without knowledge of the clinical diagnosis and the group was divided on the basis of the cytologic changes to be discussed later. The diagnoses derived from the clinical records were then compared to those obtained from the microscopic examination of the spleen.

**Results**

During the 25 years between 1940 and 1965, splenectomy for thrombocytopenia was performed at University Hospitals of Cleveland in 69 patients.

**Thrombocytopenia Associated with Drugs and Infectious Disease**

In six patients thrombocytopenia appeared to be the direct result of sensitivity to drugs, and in eight others the process was apparently related to an infectious disease. The patients with infectious disease ranged in age from 20 months to 11 years; all were white, and five were males and three females. In both the drug-induced group and that in which thrombocytopenia seemed to be related to an infectious process, the patient's response to splenectomy was immediate and dramatic with an increase in the platelet count which thereafter remained normal. The spleens in the six cases of drug-induced thrombocytopenia and in six of the eight patients in whom infectious disease was the etiologic agent were normal microscopically. In the remaining two cases the spleen had changes compatible with rubella, the underlying infection.$^{12}$ Notably, most of the splenectomies done in this group of patients were performed prior to 1950. Current practice is to delay splenectomy in such patients for six or more months.

**Thrombocytopenia Associated with Disseminated Lupus Erythematosus or of Uncertain Etiology**

After patients with infectious diseases and drug reactions were excluded from consideration, there remained 55 patients in whom no direct cause for the thrombocytopenia was suggested at the time of surgery. From the review of the clinical records and the histologic sections of the spleens, 16 of these patients are believed to have had DLE. The remaining 39 patients can only be classified as having had ITP even in the light of the long follow-up which was possible in 47 of the 55 cases.

**Disseminated Lupus Erythematosus**

Patients classified as having DLE by the clinical and histologic criteria described in this paper ranged in age from 10 to 59 years at the time of the onset of purpura. The data obtained from these patients are presented in Table 1. The disorder was limited almost entirely to women; 14 were females and two males. Four of the females were Negro. The clinical diagnosis of DLE was made when there was evidence of an inflammatory
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Table 1—Summary of Data Obtained in 16 Cases of Disseminated Lupus Erythematosus (DLE) in which a Splenectomy Was Performed for Thrombocytopenia

<table>
<thead>
<tr>
<th>Age at Onset of Symptoms</th>
<th>Preoperative Response to Steroids *</th>
<th>Response to Splenectomy †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(2 females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-40 years</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>(1 male, 8 females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(1 male, 4 females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>

* The response to steroids was considered positive if the platelet count rose to > 120,000 per mm.².
† The response to splenectomy was considered positive if the platelet count rose to > 300,000 per mm.³ postoperatively and stayed > 150,000 per mm.⁴ without therapy throughout the follow-up period.

syndrome involving multiple organ systems.³,⁴,⁵ Following the suggestion of Rabinowitz and Dameshek,⁶ the criteria for diagnosis included such major findings as arthritis, pericarditis, pleuritis, malar rash, nonhemorrhagic cerebral arterial involvement, and hemolytic anemia, with or without a positive antителlobulin test. One or more of these major criteria were present in seven of the 16 patients with DLE before splenectomy. Preoperatively in these seven patients, a variety of laboratory tests gave abnormal results; a positive LE test (4 cases), a falsely positive serologic test for syphilis (3 cases), the presence of a circulating anticoagulant directed toward the later stages of coagulation ¹³ (2 cases), a positive cephalin flocculation test without evidence of liver disease (4 cases), and a strongly positive test for antinuclear factors (7 cases).

In nine other cases, the reviewers could make a preoperative diagnosis only of ITP, yet cytologic changes suggestive of DLE were present in the spleen. In these nine cases a careful follow-up has supported the impression formed from the microscopic changes in the spleen. Six have developed clinical DLE, eight of the nine have positive LE preparations or strongly positive tests for antinuclear factors, and only one has had no clinical evidence of DLE during the 14 years since splenectomy.

Several interesting clinical observations were made in the group of patients with DLE. In only four of the 16 patients was the spleen palpated when they were first examined, and in only six was the weight of the spleen greater than that anticipated for a normal individual of the same age.¹⁴ In six of nine patients with DLE the proportion of gamma globulin was more than 20 per cent of the total serum protein, as measured by paper electrophoresis.

The period of follow-up has ranged from 12 to 168 months after surgery. Nine of the 16 patients have had repeatedly normal platelet counts for a minimum of 12 months, without resort to therapy with steroids (Table 1). Five of the seven other patients have required treatment with steroids in order to keep their platelet counts above 100,000 per mm.³ One patient remains
thrombocytopenic and is unresponsive to steroid therapy, and one patient died 5 years after the splenectomy while she still had persistent thrombocytopenia unresponsive to steroids.

The response to splenectomy in this group of patients could not be related to the duration of symptoms at the time of surgery. In nine patients who had a history of purpura for less than 1 year, a permanent remission followed splenectomy in five. Seven patients had a history of purpura for longer than 1 year and four of these underwent permanent remission. The effect of steroids has also failed to give any indication of the response to splenectomy (Table 1). Five patients responded to steroids preoperatively; three of these have had repeatedly normal platelet counts after operation. Of the four patients who failed to respond to steroids preoperatively, two remitted with splenectomy and have had repeatedly normal platelet counts.

Of particular note in this group of patients is the apparent infrequency with which the symptoms of DLE exacerbated in the months immediately after splenectomy. The possibility that splenectomy might adversely affect the cause of DLE was raised by Dameshek and Reeves but was denied by others. Evidence of lupus nephritis has appeared in only one patient, who had proteinuria before the splenectomy. The only patient who died had carcinoma of the stomach at the time of splenectomy. Although carcinoma of the stomach may be complicated by thrombocytopenia, this patient's spleen had changes characteristic of DLE, and her subsequent course, marked by fever, arthritis and the presence of a positive LE preparation, was in keeping with this diagnosis.

Pathologic changes associated with DLE: Three cytologic changes were observed in each of 14 of the 16 spleens removed from the patients with DLE. This combination was not observed in the spleens from patients with ITP or thrombocytopenia associated with the administration of drugs or infections.

1. Large mononuclear cells with prominent nucleoli were present in the germinal and primary centers and marginal zones of the follicles in DLE (Figs. 1 and 2). Cells with a similar appearance are not unusual in an active germinal center but are not commonly seen in the primary center and marginal zone.

2. Plasma cells were present in the nonfollicular white pulp of the spleen from all patients with DLE (Fig. 3). When the slides were carefully examined, abnormal forms of the plasma cell were found in all of these spleens (Fig. 4). This form of the plasma cell has also been observed in the lymph nodes of patients with DLE.

3. The third cellular change was the presence of large, nonphagocytic mononuclear cells with prominent nucleoli in the walls and sinusoids of the red pulp (Fig. 5).

One of these cytologic findings usually predominated, but only when all three were present was a diagnosis of DLE made.

In the two cases of clinical DLE in which the histologic picture was not diagnostic, abnormalities were observed but all three criteria were not satisfied. In one case, only two of the changes described were present, an increase
Fig. 1.—Illustration of a portion of a follicle and marginal zone of a spleen from a patient with DLE. Large mononuclear cells with prominent nucleoli are scattered through the marginal zone. G.C.—germinal center. P.C.—primary center. M.Z.—marginal zone. R.P.—red pulp. ------mononuclear cells. (H. and E.)

Fig. 2.—Representative illustration of the cytologic features of the mononuclear cells pictured in Figure 1. (H. and E.)
in the number of plasma cells in the nonfollicular white pulp and the presence of large, nonphagocytic mononuclear cells in the red pulp. In the other case, only an increase in the number of plasma cells in the nonfollicular white pulp was seen. Eight of the spleens in the ITP group, two of the spleens in the infectious disease group, and six of the spleens in the group in which the thrombocytopenia was associated with the ingestion of drugs also had plasma cells in the white pulp and mononuclear cells in the red pulp. None of the spleens in these three categories had mononuclear cells with prominent nucleoli in the follicles and marginal zones.

In addition to the findings which have been described, the spleens from patients with DLE always had an increase in size and number of reticuloendothelial cells and histiocytes and varying numbers of developing erythrocytes, granulocytes, and megakaryocytes. These changes were frequently seen in spleens from patients with ITP, and were therefore of no help in making the diagnosis of DLE.

Periarterial fibrosis (“onion skin”) was present in only three of the spleens from patients with DLE.
Fig. 4.—Illustration of an abnormal form of the plasma cell in the nonfollicular white pulp. These were scarce, but present in all spleens from patients with DLE. (H. and E.)

Fig. 5.—Representative illustration of the nonphagocytic, mononuclear cells in the red pulp, found in 15 of the 16 spleens of patients with DLE. (H. and E.)
Table 2.—Summary of Data Obtained in 39 Cases of Idiopathic Thrombocytopenic Purpura (ITP) in whom a Splenectomy Was Performed

<table>
<thead>
<tr>
<th>Age at Onset of Symptoms</th>
<th>Preoperative Response to Steroids *</th>
<th>Response to Splenectomy †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4 males, 16 females)</td>
<td></td>
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<tr>
<td>15-40 years</td>
<td></td>
<td></td>
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<tr>
<td>(4 males, 8 females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 40 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2 males, 5 females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals 39</td>
<td>10</td>
<td>24 ‡</td>
</tr>
</tbody>
</table>

* The response to steroids was considered positive if the platelet count rose to > 120,000 per mm.³.
† The response to splenectomy was considered positive if the platelet count rose to > 300,000 per mm.³ postoperatively and stayed > 150,000 per mm.³ without therapy throughout the follow-up period.
‡ Two of these patients were followed for only 1 month after operation.

Idiopathic Thrombocytopenic Purpura

In 39 patients in the current series, even in retrospect no diagnosis, other than ITP, seemed reasonable at the time of splenectomy either clinically or from a study of the histologic sections of the spleen. The data obtained from these patients are presented in Table 2. There were 29 females and 10 males in our series, the relative preponderance of females being similar to that reported from other centers. The preponderance of females was present at all ages, although others have noted that the sex difference was only noticeable in those patients more than 15 years old, or that no predilection for either sex occurred at any age. Only two of the patients, both females, were Negro, although University Hospitals serves a large Negro community. The relative rarity in the Negro race has been commented upon by others.

In only one of 16 patients with ITP, in whom it was measured, was the proportion of gamma globulin greater than 20 per cent of the total serum proteins measured by paper electrophoresis.

Twenty-four of the 39 patients responded to splenectomy with a rise in the platelet count to normal or above normal (Table 2). All but two of these patients have been followed from 1 to 15 years and remain in complete remission. In two patients the platelet count rose initially to levels > 300,000 per mm.³, but follow-up data for longer than 1 month after splenectomy could not be obtained.

In contrast, 15 patients did not respond satisfactorily to splenectomy. The platelet count either did not rise significantly postoperatively or rose, only to fall again after 2 weeks, in two patients, and after six years in another. Twelve of the patients were females and three were males. No follow-up data are available in three of these 15 patients. The other 12 have been followed for
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Table 3.—Effect of Duration of Illness upon the Results of Splenectomy in 39 Cases of Idiopathic Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Duration *</th>
<th>Response to Splenectomy †</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>(+) 5 (-) 2</td>
</tr>
<tr>
<td>3-12 months</td>
<td>(+) 12 (-) 5</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>(+) 7 (-) 8</td>
</tr>
</tbody>
</table>

* Time elapsed between the onset of symptoms of purpura and the splenectomy.
† The response to splenectomy was considered positive if the platelet count rose to > 300,000 per mm.³ postoperatively and stayed > 150,000 per mm.³ without therapy throughout the follow-up period.

2 to 18 years. Four patients, all females, underwent spontaneous remission 2 months to 2 years postoperatively. In two of these, remission occurred at the time of menopause, one natural and the other induced by radiation used to treat persistent menstrual bleeding. The other eight patients have persistent thrombocytopenia, but, to our knowledge, do not bleed spontaneously at the present time; they are not receiving steroid therapy.

A review of the 39 cases has not provided us with any method of predicting which patient will respond to splenectomy. We originally thought that the preoperative response to 30–80 mg. of prednisone per day would be of value. This has not proved to be the case. Of the nine patients who responded to treatment with steroids, one failed to undergo a permanent remission after splenectomy, while of the nine patients who did not respond to steroid therapy preoperatively, six had a permanent remission after splenectomy. Another facet which was examined was the duration of symptoms prior to the surgical procedure. These data are presented in Table 3. Although the numbers are small, they suggest that an illness of more than 1 year's duration is perhaps less likely to respond to splenectomy than one of shorter duration.

None of the patients in the ITP group has developed DLE subsequently, but two females have weakly positive reactions for antinuclear factors. Neither patient has clinical evidence of DLE nor a positive LE test.

Eight of the 39 patients (20 per cent) had palpable spleens when first examined. Four of these patients were under the age of 15 years. There was no statistical difference between the spleen weights in the DLE group and those in the ITP group.

In some cases, the histologic appearance of the spleens removed from patients with ITP was normal, while in others there was an increase in reticuloendothelial cells and histiocytes and varying numbers of hematopoietic elements (i.e., erythrocytes, granulocytes, and megakaryocytes). "Lipid-laden histiocytes" were observed in six of the spleens, but no effort was made to utilize other methods for their identification. In this series, they were not observed in the cases of secondary thrombocytopenia, regardless of cause. There was no correlation between the presence or absence of any of the cellular elements and the clinical course of the patients.
DISCUSSION

The present study is a review of the experience with splenectomy at University Hospitals of Cleveland in 69 patients in whom the operation was done primarily because of thrombocytopenia. The group included 14 patients who manifested thrombocytopenia as a result of an infectious process or an idiosyncratic reaction to an ingested drug. After these patients were excluded, there were 16 patients in whom the thrombocytopenia was associated with DLE and 39 patients in whom the thrombocytopenia could only be classified as idiopathic since no other underlying cause has appeared in long-term follow-up.

It has been known for many years that DLE can be associated with thrombocytopenia which may be indistinguishable from ITP. This complication may precede the clinical picture of DLE, and to date there has been no reliable method for identifying those patients who will eventually have clinical DLE. The present study provides criteria, which have been reliable in our experience, for the diagnosis of DLE by histologic examination of splenic tissue. These changes consisted of the presence of large mononuclear cells with prominent nucleoli in the follicles and marginal zones, plasma cells in the nonfollicular white pulp, and nonphagocytic mononuclear cells in the walls and lumens of the sinusoids of the red pulp. These three changes were present in the spleens of 14 of the 16 patients with DLE.

The clinical data obtained in the patients with DLE are quite similar to those reported by others. In six of nine patients in whom a paper electrophoresis of the serum proteins was carried out, the gamma globulin fraction was more than 20 per cent of the total protein, while in ITP the gamma globulin was present at these high concentrations in only one of 16 patients, suggesting the usefulness of this criterion in differential diagnosis. Nine of the 16 patients had a permanent remission of their thrombocytopenia after surgery. We were unable to predict from the response to steroids or the duration of the illness before surgery which patients would undergo a permanent remission. Only one of the 16 patients has developed renal complications. The low incidence of nephritis in this group is somewhat surprising in light of the incidence of lupus nephritis noted by others. Perhaps the rather benign course followed by these patients is a manifestation of an altered immunologic response due to the absence of the spleen, as suggested by Best and Darling, who also noted the good prognosis in their patients with DLE following splenectomy.

A permanent remission followed splenectomy in 24 of the 39 patients with ITP, in agreement with reports in which this response is usually said to occur in 50 to 80 per cent of cases. There were few Negroes in our group, in agreement with the reports of others. The spleen was palpable in 20 per cent of our cases and does not exclude the diagnosis of ITP. There were no reliable criteria for predicting in advance which patients would undergo permanent remission after splenectomy, a finding in agreement with the experience of others. Our data suggest that when chronic ITP has its onset at the extremes of life, the prognosis for response...
splenectomy is not as favorable as when the illness commences in middle life. Our experience with children is somewhat different from that reported by Newton and Zuelzer, since they point out a better chance of cure in the childhood group. Perhaps this difference can be explained by the method of selection of our patients, for all cases in which thrombocytopenia could be related to infection or the ingestion of drugs and all cases in which a spontaneous remission occurred without splenectomy were excluded. In addition, we related the response to splenectomy to the time of the onset of purpura rather than to the time the patients were first seen by a physician. Thus, some patients in whom splenectomy was not performed until adult life were believed to have had the disorder since childhood.

The delay between the onset of symptoms of ITP and splenectomy was of some help in predicting the outcome. Of the 24 patients in whom the illness had been present less than one year, 17 responded to splenectomy with a permanent remission. In the 15 patients who had an illness of greater than a year's duration, only seven underwent a permanent remission postoperatively.

The histologic and cytologic changes in the spleens from patients with ITP and secondary thrombocytopenia were similar to those described in previous reports. These changes consist of enlargement of the germinal centers, dilation of the sinusoids of the red pulp, and the presence of varying numbers of megakaryocytes, eosinophils, and neutrophils. None of these changes is specific for thrombocytopenia, and none of the described findings has been helpful in the differential diagnosis between ITP and the thrombocytopenia associated with DLE. Periarterial fibrosis ("onion skin") has been said to be diagnostic of DLE when found in the spleen. In our series this change was present in only three of the spleens from patients with DLE. More recently, "lipid-laden histiocytes" have been observed in spleens from patients with ITP and secondary thrombocytopenia. This latter change may be more helpful. It was not observed in the spleens from patients with DLE in this series.

This investigation has provided criteria for the diagnosis of DLE from histologic sections of the spleen before the diagnosis becomes evident clinically. This may be of some help in management since one can be prepared for the eventual onset of DLE so that its complications can be treated at an earlier stage.

SUMMARY

Sixty-nine cases of thrombocytopenia in which splenectomy had been performed have been reviewed. New cytological criteria are described for the diagnosis of disseminated lupus erythematosus by the examination of the splenic tissue.

Six cases of thrombocytopenia associated with the ingestion of drugs and eight with infectious diseases responded promptly and permanently to splenectomy. The thrombocytopenia associated with disseminated lupus erythematosus (in 16 cases) and idiopathic thrombocytopenic purpura (in 39 cases)
had a much more variable response. Approximately three-fifths of patients in each group had a remission sustained for at least 12 months following splenectomy. In general those patients who had thrombocytopenia for more than one year before surgery were less likely to respond to splenectomy.

SUMMARIO IN INTERLINGUA

Es presentate un revista de 69 casos de thrombocytopenia in le quales splenectomia habeva essite effectuate. Nove criterios cytologic es describite pro le diagnose de disseminate lupus erythematosose a base del examine del tissu splenic.

Sex casos de thrombocytopenia associate con le ingestion de pharmacos e octo associate con morbo infectiose respondeva prompte- e permanentemente a splenectomia. Le thrombocytopenia associate con disseminate lupus erythematosose (16 casos) e idiopathic purpura thrombocytopenic (39 casos) respondeva multo plus variatemente. Approximativemente tres quintos del patientes in cata-un del duo gruppos habeva un remission perdurante 12 menses o plus post le splenectomia. A generalmente parlar, patientes in qui le thrombocytopenia habeva essite presente durante plus que un anno ante le chirurgia habeva un prognose de successo chirurgic minus favorabile que le alteres.

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