Splenic pathology in immune thrombocytopenia

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SUMMARY Splenic pathology was analysed in 73 patients with immune thrombocytopenic purpura who underwent splenectomy for bleeding that had been resistant to adrenocorticosteroids. The mean splenic weight was 100 g. The only notable macroscopic feature was the prominence of Malpighian corpuscles in 15 cases. Microscopic examination showed formation of germinal centres in the lymphoid tissue of the white pulp in 40 cases, prominence of the histiocytes in the red pulp in 18 cases, and infiltration with neutrophils in the same area in 49 cases. Myeloid metaplasia throughout the splenic tissue was minimal in 58 cases, moderate in 15, and extreme in two. No distinguishing features were found in the spleen from patients who had not received previous immunosuppressive treatment ($n = 3$), those treated with prednisone (1 mg/kg/day) for a median of 14 days ($n = 62$), or those who had received the same dose of prednisone and additional azathioprine or cyclophosphamide (2 mg/kg/day) for a median of four weeks ($n = 8$). No correlation could be shown between histological features and the age of the patient or titre of antiplatelet antibodies. Similarly, no distinguishing features were found in patients with associated systemic lupus erythematosus ($n = 8$), hyperthyroidism ($n = 6$), immune haemolysis ($n = 3$), or recent viral illness ($n = 3$).

The typical histological features of spleens removed from patients with idiopathic immune thrombocytopenia are reported to be lymphoid hyperplasia with formation of germinal centres, infiltration of the splenic cords with granulocytes, and variable proliferation of histiocytes in the red pulp.¹⁻⁴ In addition, splenic haematopoiesis of minimal degree has been described, although it is unusual for this to be a prominent feature; in rare cases it may reach a degree comparable with that seen in the myeloproliferative syndrome.⁵ This study re-examined splenic pathology in patients with immune thrombocytopenia, focusing on the range of myeloid metaplasia that may occur and seeking histological correlations with the previous administration of adrenocorticosteroids or other immunosuppressive drugs that are potential modifiers of splenic histology,⁶ the titre of antiplatelet antibody, the age of the patient, and the presence of underlying systemic disorders that may be associated with secondary immune thrombocytopenia.

Material and methods

The spleens from 73 patients diagnosed as having

immune thrombocytopenia were reviewed. All subjects fulfilled the criteria for this diagnosis⁷ and were managed according to a standard protocol whereby splenectomy was undertaken for symptomatic refractory thrombocytopenia after treatment with adrenocorticosteroids alone for a median of two weeks (group 1, $n = 62$); after treatment with adrenocorticosteroids combined with azathioprine for a median of four weeks (group 2, $n = 8$); or after all previous treatment had been refused (group 3, $n = 3$). Patients with associated lymphoproliferative disorders were excluded. Included were patients with systemic lupus erythematosus ($n = 8$), hyperthyroidism ($n = 6$), immune haemolytic anaemia ($n = 3$), and recent viral illnesses ($n = 3$).

Table 1 shows the distribution of the patients by age and sex. The clinical details and response to treatment of the 148 patients from whom the subgroup undergoing splenectomy were drawn are available from PJ.⁸ All spleens were weighed and examined macroscopically immediately after surgery and samples selected for histological examination after fixation in buffered 10% formol saline. Sections were stained with haematoxylin and eosin and, using a simple scoring system, were assessed for the degree of lymphoid hyperplasia, infiltration by granulocytes, histocytic proliferation, and splenic

Table 1 Details of patients and methods of treatment

Group	No in group	Median age and sex	
		M/F	(years)
Group 1 (splenectomy alone)	3	0/3	33
Group 2 (prednisone and splenectomy)	62	15/47	34
Group 3 (prednisone with immunosuppressives and splenectomy)	8	1/7	35

extramedullary haematopoiesis or myeloid metaplasia.

The presence of systemic lupus erythematosus was confirmed serologically,^{8,9} hyperthyroidism as previously described,¹⁰ and membrane associated immunoglobulin by established techniques.¹¹

Results

MACROSCOPIC APPEARANCE

The splenic weights varied from 5 to 470 g, with a mean of 100 SD (40) g. The gross appearance was normal in 48 cases. Sixteen cases showed prominence of the Malpighian corpuscles, four were congested, and three had a “beefy” cut surface. No differences were apparent between the three treatment groups or in the spleens removed from patients with idiopathic, as opposed to secondary immune, thrombocytopenia.

HISTOLOGICAL FEATURES

Lymphoid tissue varied considerably in quantity, as did the number of germinal centres in the white pulp. The germinal centres were absent in 33

spleens, and common (17) to very common (one) in only 17 cases (Fig. 1).

Histiocytes were normally distributed in 18 spleens. Thirty seven cases showed aggregates of foamy histiocytes, resembling lipogranulomas in or adjacent to the white pulp (Fig. 2): these are a common incidental finding in normal spleens. A moderate (13) to high (5) diffuse proliferation of histiocytes in the red pulp was noted in 18 cases (Fig. 3).

Neutrophils infiltrated the red pulp variably. No increase in numbers was noted in 24 cases. In 30 cases granulocytes were seen to be concentrated in the red pulp immediately surrounding the lymphoid tissue. 19 cases exhibited a more diffuse infiltration throughout the cords of the red pulp.

Haematopoiesis was either absent (19 cases) or limited to an occasional megakaryocyte or early myeloid cell in 39 cases. More extensive extramedullary haematopoiesis was present in 15 spleens (13 with moderate evidence, two high), and in two this reached the degree usually encountered in the myeloproliferative syndrome,¹² in which groups of erythroblasts, myeloid precursors, and megakaryocytes were present in the sinusoids (Fig. 4). Occasional haematopoietic cells were also noted in the splenic cords.

CORRELATION WITH TREATMENT

In none of the three treatment groups were distinctive histological features present. Specifically, neither the two week course of adrenocorticosteroids that preceded splenectomy (n = 62) nor the four week course of adrenocorticosteroids combined with immunosuppressive agents (n = 8) produced

Fig. 1 Well delineated reactive germinal centre present in splenic white pulp from patient with immune thrombocytopenia. (Haematoxylin and eosin.) x100.

Fig. 2 Striking lipogranuloma located adjacent to splenic white pulp. (Haematoxylin and eosin.) x400.

discernible differences in splenic pathology (Table 1).

EFFECT OF AGE

The distribution of age was not strikingly different between the three groups, and no correlation was recognisable with any of the histological features.

INFLUENCE OF ANTIBODY TITRE

When measured, concentrations of antiplatelet membrane associated immunoglobulin were consistently raised in patients with immune thrombocytopenia who failed to respond to adrenocorticosteroids with or without additional immunosuppressive agents. Falling titres of this antiplatelet antibody were associated with remission in clinical bleeding and increased platelet counts, so that these patients would not have undergone splenectomy. Nevertheless, no correlation between splenic histopathology and antibody titre could be found.

SECONDARY IMMUNE THROMBOCYTOPENIA

Spleens removed from patients with systemic lupus erythematosus, hyperthyroidism, associated immune haemolytic anaemia, or viral disease showed histological features that were indistinguishable from those of the spleens removed from patients with idiopathic immune thrombocytopenia.

Discussion

Immune thrombocytopenia, whether idiopathic or secondary to underlying disease but specifically

excluding lymphoproliferative disorders, was treated initially with adrenocorticosteroids⁷ and in refractory patients by splenectomy. In this series of 73 patients spleens that had been removed because of immune thrombocytopenia resistant to drug treatment showed considerable variability in histological change.

Three points are germane to this discussion. Firstly, the classically described features of proliferation of lymphoid germinal centres and neutrophilic infiltration in the spleens of patients with immune thrombocytopenia¹⁻⁴ could not be shown consistently in the present study. Secondly, although diffuse proliferation of foamy histiocytes has been reported to be a feature associated with a systemic response to treatment,¹³ many of the spleens from patients in the present study failed to show this feature. The most likely explanation for this discordant observation is the short time during which our patients received medical management with adrenocorticosteroids before splenectomy.

Finally, although the presence of extramedullary haematopoiesis in the spleen has been previously reported¹⁴ the present survey indicates that such myeloid metaplasia is usually limited to the presence of occasional megakaryocytes or metamyelocytes in the sinusoids. The prevalence of moderate to high amounts of haematopoietic tissue in the spleen was far lower than has been reported before.^{3,5} In addition, this tissue was situated mainly in the sinusoids, with only occasional cells visible in the splenic cords. Such a pattern could not be distinguished from that which occurs in the myeloproliferative syndrome.

Fig. 3 Photomicrograph illustrating diffuse proliferation of foamy histiocytes in spleen. (Haematoxylin and eosin.) $\times 100$.

Fig. 4 Illustration of extensive extramedullary haematopoiesis with prominent megakaryocyte and erythroblasts present within sinusoids of spleen in immune thrombocytopenia. (Haematoxylin and eosin.) $\times 400$.

Our observation contradicts previous reports showing the haematopoietic tissue to be limited to the extravascular space of the splenic cords in patients with immune thrombocytopenia, whereas in myelofibrosis the haematopoietic cells were distributed equally between the cords and sinuses of the red pulp.⁵

This experience does not support the existence of reliable diagnostic criteria for distinguishing the pattern of haematopoiesis in spleens removed from patients with immune thrombocytopenia, myeloproliferative syndrome, or other infiltrative lesions of the bone marrow. Thus in view of the rarity of extensive splenic haematopoiesis in immune thrombocytopenia we recommend that such patients be investigated carefully to exclude the possibility of coincidental myeloproliferative syndrome or other underlying disorders.

These findings confirm the presence of generally minimal extramedullary haematopoiesis in the spleen of patients with immune thrombocytopenia and emphasise the rarity with which this reaches a degree comparable with that found in the myeloproliferative syndrome. Furthermore, our observation that splenic histopathology in patients with immune thrombocytopenia, whether idiopathic or secondary, is not modified by previous adrenocorticosteroid or immunosuppressive treatment is at variance with earlier reports but may in part be explained by the short period of medical management that our patients received before undergoing splenectomy.

Finally, in patients with immune thrombocytopenia no distinguishing features were present on histopathological criteria that could be correlated with antiplatelet antibody titres or with systemic lupus erythematosus, hyperthyroidism, immune haemolysis, or viral disease. In particular, the perivascular onion skin fibrosis and degenerative changes in the capsular collagen described in systemic lupus erythematosus were not shown.¹⁵

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