HYPERSPLENISM ASSOCIATED WITH FOLLICULAR LYMPHOBLASTOMA

REPORT OF A CASE WITH SPLENECTOMY

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In diseases affecting the reticulo-endothelial system, involvement of the spleen may result in serious hematologic disturbances requiring immediate treatment. Reports of secondary, or symptomatic hypersplenism with isolated or combined cytopenias of the peripheral blood include diagnoses of hepatic cirrhosis, Felty's and Banti's syndrome, infectious splenomegalies, lipoid storage diseases, Boeck's sarcoidosis, leukemias, Hodgkin's disease and reticulum cell sarcoma.

This report deals with an instance of secondary hypersplenism due to follicular lymphoblastoma of the spleen, with thrombocytopenic purpura and neutropenia, the latter being sufficient to require splenectomy which was followed by a rise in the platelet count and clinical improvement due to cessation of purpura. Certain findings in the blood, bone marrow and spleen are discussed in the light of recent studies dealing with the general problem of hypersplenism.

CASE REPORT

On May 21, 1947, the patient, a white male 16 years old, was admitted to the Veterans Administration Hospital, Dearborn, Michigan, because of bleeding, tender, swollen gums, and malaise. He had felt well until two days before admission. Examination showed swollen, spongy, bleeding gums, hyperemia of the pharynx, petechiae of the skin, enlarged cervical, axillary and inguinal lymph nodes, and an enlarged spleen extending 14 centimeters below the costal margin. There was a chain of lymph nodes, including a mass 3.5 centimeters in diameter, in the left anterior cervical region; a similar chain with a mass two centimeters in diameter was present on the right side. The axillary nodes were 1 to 2.5 centimeters in diameter. Those in the inguinal region were smaller.

The capillary fragility, tested in the upper extremities, was considerably increased. The coagulation time was normal and the bleeding time was prolonged. The blood counts were: erythrocytes, 5,200,000; leukocytes, 3,900; platelets 51,000 (normal range by the method used is 150,000 to 350,000). The differential distribution of the leukocytes was: neutrophils 7 per cent; monocytes 11 per cent; lymphocytes 72 per cent. Sternal marrow study on May 29, 1947 was summarized as follows: "The marrow is hyperplastic, due chiefly to increased granulopoiesis. There is no evidence of leukemia. Megakaryocytopoiesis is increased, with a relative increase in the incidence of immature forms. There are numerous lymphocytes of reticulum origin and, in view of the enlargement of lymph nodes and spleen, the possibility of lymphoblastoma must be considered. Biopsy of an axillary lymph node is indicated."

On June 6, 1947 biopsy of an axillary lymph node revealed lymphoblastoma, follicular type (fig. 1). The hematologic findings in this patient are shown in chart 1. On the basis of peripheral neutropenia and thrombocytopenia in the presence of increased granulopoiesis and megakaryocytopoiesis in the marrow, with enlargement of the spleen, the working diagnosis was secondary hypersplenism due to follicular lymphoblastoma of the spleen.

Roentgen irradiation therapy over the splenic region was recommended for treatment of the lymphoblastoma and in the hope that it might also reduce the splenic effect on the hematologic equilibrium. Within three days after irradiation of the spleen there was a fall in the counts of all cellular elements.
of the peripheral blood. Before therapy the blood counts were: erythrocytes, 4,300,000; leukocytes, 5,900; platelets, 46,000. Afterwards the counts were: erythrocytes, 1,900,000; leukocytes, 1,900; platelets 13,000. The fall in erythrocytes was not associated with hemorrhage or jaundice. Unfortunately, facilities for quantitative urobilinogen studies were not available, so that the question of a hemolytic episode could not be investigated. However, as there was no evidence of bleeding, an erythroclastic effect of irradiation was considered possible. After the patient had received transfusions of 1,750 cubic centimeters of whole blood during a period of six weeks, the erythrocyte count was normal. Neutropenia and thrombo-
cytopenia persisted, but the purpura gradually subsided. On July 2, 1947, the second sternal marrow study showed changes practically identical with those seen previously.

**Chart 1.** Effect of injection of 1 cc. of epinephrine subcutaneously on peripheral neutrophil and platelet counts and the size of the spleen

*Fig. 1.* Spleen, showing replacement of normal parenchyma by neoplastic follicular masses

In spite of persistent neutropenia and thrombocytopenia, the patient remained comfortable and asymptomatic until July 16, 1947, when severe purpura reappeared. As there was no cessation of purpura during the following two weeks, splenectomy was advised. The adrenalin test, recommended by Doan and Wright 4 for evaluating the role of the spleen in the production of the hematologic changes in patients
with hypersplenism, was carried out with the results shown in chart 1. Injection of adrenalin was followed by contraction of the spleen and rises in the neutrophil and platelet counts. We did not consider the changes significant, but they were of the magnitude observed by Doan and co-workers and interpreted by them as evidence of sequestration of leukocytes and platelets in the spleen. Splenectomy was performed August 8, 1947. The spleen weighed 1,314 grams and presented a nodular appearance because of the presence of discrete, translucent gray masses from one-half to two centimeters in diameter. The histologic diagnosis was follicular lymphoblastoma of the spleen (figs. 2 and 3). Cytologic details of the changes in the spleen are discussed below. Three days after splenectomy all evidence of purpura had disappeared; the capillary fragility and bleeding time had become normal.

In addition to those already mentioned, two other marrow studies were made. The third study on August 17, 1947, nineteen days after splenectomy, revealed slight relative increase of leukogenesis (myeloid erythroid ratio 7:1), and normal megakaryocytogenesis. The fourth study on July 28, 1948, almost one year after splenectomy, revealed completely normal findings. Except for a single brief episode of slight purpura of the skin in December 1947, the patient has been in excellent general health and free of purpura, although neutropenia persists. During the postoperative period of approximately one year there has been a slight increase in the size of several of the cervical lymph nodes. The patient is receiving roentgen irradiation therapy at present.

**Discussion**

The material available for study includes numerous blood data and smears, aspirated sternal bone marrow obtained before and after splenectomy, histologic sections and imprints from the diseased lymph nodes and spleen. The findings will be applied to the various points of current disagreement concerning the blood, bone marrow and splenic changes in hypersplenism.

*Peripheral blood.* In this patient with apparent secondary hypersplenism, the
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Peripheral blood manifestations were neutropenia and thrombocytopenia. Furthermore, the marrow findings indicated hyperplasia of the elements deficient in the blood, thus satisfying an important criterion for the diagnosis of hypersplenism.\textsuperscript{30,3}\textsuperscript{a}

The chief point of interest is the dissociation between the platelet and granulocytic responses to splenectomy. While the thrombocytopenia disappeared, severe neutropenia persisted, even though the marrow reverted to normal from an initial hyperplasia of both granulocytic and megakaryocytic elements. It is difficult to explain this dissociation on the basis of current widely accepted concepts of the mechanism of the splenic effect in cases of hypersplenism. If the adrenalin test has any significance, it would indicate that, in this patient, there was excessive sequestration of both neutrophils and platelets in the hypertrophied spleen. After removal of the spleen, one would expect an effect on both neutrophils and platelets.

On the other hand, the hyperplastic appearance of the marrow before splenectomy may represent inhibition of maturation of neutrophils and platelets due to the activity of an inhibitory hormone of splenic origin.\textsuperscript{3,3} It is noteworthy that, even after the marrow had become normal following splenectomy, the neutrophil count in the blood remained depressed. The removal of the inhibitory factor on neutrophilic leukogenesis did not result in correction of the peripheral neutropenia. The neutropenia in this case may be unrelated to the action of the hypothetical splenic hormone.

Bone marrow. Recently, Dameshek and Miller\textsuperscript{3,3} have presented data which they regard of importance for distinguishing between the marrow pattern in idiopathic thrombocytopenic purpura and that seen in symptomatic or secondary hypersplenic thrombocytopenia. In idiopathic thrombocytopenic purpura they found that the megakaryocytes were increased over normal, but showed great diminution of platelet formation, whereas in secondary hypersplenic thrombocytopenia the megakaryocytes were increased over normal, but platelet production was also normal. They accounted for the low platelet count in the blood in secondary cases by postulating inhibition of delivery of platelets from the marrow to the blood. We were unable to support this concept in our case. There was no accumulation of undelivered platelets in the marrow before splenectomy, and the platelet content of the marrow was greatly diminished before splenectomy. Our enumerations of platelet-producing megakaryocytes before and after splenectomy are compared with the data presented by Dameshek and Miller in table 1. The quantitative marrow findings in our case of secondary purpura are clearly indistinguishable from those characterizing the essential or idiopathic form of hypersplenic thrombocytopenic purpura.

Spleen. The histologic and cytologic findings in the spleen in patients with primary and secondary hypersplenic thrombocytopenia are obscure. Some observers have reported excessive phagocytosis of platelets,\textsuperscript{10} but others consider such findings as unconfirmed.\textsuperscript{3,3} Moeschlin\textsuperscript{3} observed that splenic puncture material revealed a smaller incidence of macrophages in spleens from primary and secondary thrombocytopenic purpura than he was accustomed to finding in puncture material from spleens of other conditions not associated with thrombocytopenia. Hertzog\textsuperscript{3}
studied histologic sections of spleens from 36 autopsied cases of essential thrombocytopenic purpura, reporting a fairly normal structure in the series. Hirschboeck\(^7\) obtained imprints of the spleen in a case of secondary hypersplenism associated with the Felty syndrome, reporting that about half the reticulo-endothelial cells revealed evidence of phagocytosis and digestion of other cells.

Unfortunately, such phagocytic activity of the reticulum cells of spleens in various diseases is of common occurrence. Furthermore, the finding of more platelets in smears of imprints of spleen than is the case for peripheral blood is not good evidence of excessive sequestration of platelets, since it has been established that this situation prevails in splenic material in various conditions other than thrombocytopenia.\(^8\) With one exception, we know of no recent attempts to quantitate the degree of phagocytosis or sequestration of the various cellular elements concerned in the peripheral cytopenias. Von Haam and Awny\(^9\) studied sections and smears of spleens from 32 patients with secondary hypersplenic cytopenias. These authors have made several important conclusions: namely, (1) the phagocytic power of the enlarged spleen in secondary hypersplenism is not excessively increased, (2) phagocytosis of the deficient blood elements was not convincingly excessive, and (3) blood destruction in the hyperplastic spleen cannot be explained by the process of phagocytosis alone. They particularly emphasized the finding of small clusters of the deficient blood elements in various degrees of disintegration throughout the pulp and sinusoids of the spleen.

In our case, sections of the spleen revealed a slight increase in the incidence of eosinophil and neutrophil granulocytes. We were unable to identify disintegrating platelets, nor were we able to find the cytolical foci described by Von Haam and Awny. The imprints of spleen provided excellent specimens for the study of platelets as well as leukocytes. It was possible to identify disintegrating cells with ease and, in addition, we found occasional free platelets lying in the pulp and sinusoids as well as some platelets superimposed upon, or phagocytosed by both reticulum cells and large lymphoid cells. It may be stated that the spleen in our case contained an accumulation of platelets which we presume to have been removed from the blood circulating through that organ, as there was no evidence of the forma-

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<td>Normal individuals*</td>
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<td>Acute idiopathic thrombocytopenic purpura*</td>
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<td>51-72</td>
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Accumulation of platelets in the spleen. However, the significance of this finding is unknown (and we believe that this is true of the reported findings in previous studies) as there is as yet no reliable method for quantitating the platelet content of the spleen. Since accumulation of platelets is characteristic of spleens in various conditions other than thrombocytopenia, we are hesitant to accept the phagocytic or sequestration theory as completely satisfactory explanation of the peripheral deficit of platelets. It is possible that the conflicting views on the subject are the result of the operation of several factors to varying degrees in different cases. We see no reason, at present, for considering the phagocytic or sequestration theory as exclusive of the concept of a hormonal, or at least humoral, mechanism of the production of thrombocytopenia in hypersplenic conditions.

SUMMARY

A patient with secondary hypersplenism due to follicular lymphoblastoma of the spleen exhibited neutropenia and thrombocytopenia, the latter being of sufficient severity to require splenectomy.

Splenectomy was followed by clinical improvement due to restoration of the platelet count and cessation of purpura, whereas the neutropenia persisted.

The significance of the blood, bone marrow, and splenic findings is discussed in the light of current concepts of the mechanism of the hypersplenic effect on the peripheral blood picture.

REFERENCES

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