CASE REPORT

Hypersplenism

A Case Report with Postmortem Study

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Splenic hyperactivity as the basis of a hematologic disorder was first suggested by Gretzel almost a century ago. Since then Banti, as well as numerous other authors, has confirmed the impression that the spleen might be responsible for the reduction in the circulating red cells found in "splenic anemia." Kaznelson, in 1916, added thrombocytopenic purpura to the list of splenic cytopenias. The frequent occurrence of leukopenia in splenic anemias was noted by Osler as well as others.

Frank in 1916 postulated that overproduction of a splenic hormone might be responsible for both anemia and leukopenia. From a study of post-splenectomy patients, Dameshek and colleagues in 1941 suggested that several "hypersplenic" syndromes might be possible, with decrease in all circulating elements of the blood stream, or selected ones. At about this same time Doan and his group demonstrated clinically by splenectomy that the relationship between the splenic enlargement and the cytopenia was a causal one. This group of workers established the entity of "primary hypersplenism," limiting it to those cases in which splenic hyperactivity, with or without splenomegaly of unknown etiology, produced a depression of one of the three circulating elements of the blood.

Under this heading is now included primary splenic neutropenia, primary splenic panhematopenia, idiopathic thrombocytopenic purpura, and congenital hemolytic anemia.

Separable from this primary category is a group of cases in which splenomegaly of known cause is associated with a cytopenia. This syndrome has been described in Gaucher's disease and in various other conditions. The cytopenias in these cases have at times responded to splenectomy, thus allowing their inclusion in a category of secondary hypersplenism. Felty's syndrome, consisting of the association of leukopenia, occasionally anemia, chronic rheumatoid arthritis, and enlargement of the spleen, has been considered by many authors to represent hypersplenism with associated arthritis. It is controversial whether this is a primary hypersplenism with associated arthritis or hyperfunction secondary to the splenomegaly of rheumatoid arthritis.

To this day the clinical entity of hypersplenism remains difficult to delimit. For the most part, it is agreed upon that the ultimate criterion for the diagnosis of this condition is the demonstration that splenectomy favorably affects the existing cytopenia.

While many clinical reports are available, to date the pathologic data are rather meager. Most of the descriptions are based upon bone marrow aspirations and surgically removed spleens and lymph nodes. A review of the litera-
The literature reveals postmortem studies on one case of primary hypersplenism and several cases of Felty’s syndrome. The most extensive anatomic report by Von Haam is based upon surgically removed spleens. The following case is offered as a complete study of the hematopoietic system in an instance of splenic panhematopenia associated with rheumatoid arthritis. Hyperplastic changes affecting the entire reticulo-endothelial system, and striking white as well as red cell phagocytosis, make this case somewhat unique. The further demonstration of a circulating substance which would lyse white cells on contact is of interest in considering the mechanism of hypersplenism.

**CASE PRESENTATION**

**First Admission**

A 57-year-old white shipyard foreman was admitted to the Dental Service of the Boston City Hospital on February 27, 1951 for an alveolar infection following a tooth extraction one week before. A WBC of 1,100/cu. mm. of blood was discovered, and the patient transferred to a medical service. He gave a history of some shortness of breath on exertion and a weight loss of 50 lbs. in the preceding six months. Four months prior to admission he had had a three week illness characterized by fever, chills and cough, diagnosed by his family physician as “virus pneumonia.” He continued to have a mild cough, progressive weakness and anorexia until the time of his admission. In his position as dock foreman, exposure may have occurred to organic solvents, greases and paints, depending on the cargo loaded.

The past history included an attack of migratory polyarthritis nine years ago, diagnosed by his physician as rheumatic fever. He was confined to bed for several weeks at that time. Since then there had been progressive flexion deformity of his right hand. Serologic lues was discovered two years prior to admission and was treated with a two week course of penicillin.

On admission he appeared pallid, emaciated, and chronically ill. The blood pressure was 110/70, temperature 99.8, pulse 86, and respiration rate 26. No icterus was seen. There was a gray-based, 2.0 x 3.0 cm. ulceration of the left lower gum and subhyaloid region, with a tender submaxillary node. The heart was not enlarged, but an accentuated M, was heard, with a grade II blowing systolic apical murmur. Liver dullness was detectable two finger breadths below the costal margin, and the spleen was palpable three finger breadths below the costal margin. Neurologic examination was negative. Several small, freely movable inguinal nodes and solitary small bilateral axillary nodes were felt. Ulnar deviation of both hands with a flexion deformity of the right was present.

**Laboratory Examination**

RBC 3.9, Hgb. 8.2, Retic. 2.3, WBC 500, differential-segmented polys 0, bands 5, L. 82, M. 11, E. 2. MCV 70, MCHC 30, MCH 21. Platelets appeared decreased. The icteric indexes were 4 and 5. Urinalysis was not remarkable. The Hinton test was positive on two occasions. Liver function tests showed a consistently 4 plus cephalin flocculation. Two blood cultures were sterile. An upper G-I series and a metastatic series were within normal limits. Two bone marrow aspirations showed an absence of mature polymorphonuclear leukocytes, but otherwise active granulocytic and erythroid series. The myeloid-erythroid ratio was 3.6/1.

He received 5 units of blood with much improvement and was discharged on March 1, 1951, with a Hgb. of 10.6 Gm./100 cc. of blood, and a WBC of 600 cu. mm. of blood. The diagnosis was considered to be hypersplenism with anemia and leukopenia (Felty’s syndrome). Splenectomy had been offered, but was refused.

**Second Admission**

He was readmitted three months later on June 30, 1951 for transfusion. He had become progressively weaker after discharge. The spleen was now palpable four finger breadths...
Laboratory Examination

RBC 3.2, Hgb. 5.9, WBC 1500, differential-segmented polyps 38, bands 2, L. 54, M. 6. Icteric index was 1. A strong leukocidin was demonstrated in the blood. The patient's serum was shown to produce rapid lysis of added normal white cells in the presence of complement.* No rheumatoid changes were noted in the hands by x-ray.

Third Admission

On August 17, 1951, one and one-half months later, the patient was admitted to an outside hospital for the same complaint of weakness. A chest film now showed a diffuse area of consolidation involving mainly the superior segment of the left lower lobe, considered possibly to be tumor. Bronchoscopy demonstrated only purulent material coming from the left upper lobe main stem bronchus. Tuberculin tests were negative. A liver biopsy to rule out lymphoma was reported as normal.

Laboratory Examination

RBC 2.8, Hgb. 8.6, WBC 500, differential-segmented polyps 24, bands 4, L. 72, rare normoblast, platelets 70,000. Retic. 1.3.

Antibiotics were administered for the respiratory infection, and transfusions were given. A diagnosis of lymphoma, type undetermined, was made.

Fourth Admission

He was readmitted to the Boston City Hospital as a transfer from the above hospital on August 31, 1951. Findings on physical examination were the same as on earlier admissions, save for coarse inspiratory rales at the left base. Chest films were as above.

Laboratory Examination

RBC 1.9, Hgb. 5.2, WBC 1250. The icteric index was 15. Leukocidin could no longer be demonstrated. During one of several transfusions he had a mild reaction, and some difficulty was experienced in cross-matching his blood. A low-grade temperature, associated with a urinary tract infection, was present during this admission. In spite of penicillin therapy, the urinary infection became more severe, he went gradually downhill, and expired on September 19, 1951.

Postmortem Findings

An autopsy was performed 21 hours postmortem. The body showed evidence of considerable weight loss. There was marked pallor, especially of the mucous membranes, but no icterus was noted. A few freely movable axillary and cervical nodes were present, all under 1.0 cm. in diameter. Several 0.5 to 1.0 cm. subcutaneous nodules were found on the upper extremities, appearing like small abscesses when cut. Flexion deformity of the right hand was seen as described clinically. There was 300 cc. of cloudy yellow ascitic fluid and 150 cc. of similar fluid in each pleural cavity. The heart weighed 340 Gm. and was not remarkable, showing no evidence of rheumatic stigmata. The lungs were emphysematous, with an area of red-gray, firm consolidation in the left mid-lung field. The spleen weighed 780 Gm. and was moderately firm in consistence with a smooth capsule, not appearing thickened. There was a raised, firm, yellow, 3.5 cm. infarct at the upper pole, sharply demarcated from the surrounding tissue. Several smaller infarcts were scattered around the large one. The parenchyma had a homogeneous, firm, red-brown appearance in which areas suggestive of follicles were barely distinguishable. The liver weighed 1,550 Gm. and showed only conges-
tive mottling. The combined weight of the kidneys was 300 Gm. They had finely granular surfaces with scattered groups of yellow, 1.0 mm., abscesses. There were many 0.5 to 1.0 cm., yellow abscesses throughout the cut section, and yellow streaking of the papillae. No dilatation of pelves or ureters was found. Abscesses 1.0 cm. in diameter were present in both lateral prostatic lobes, but no other nodularity or masses were seen. Vertebral, costal, sternal and mid-shaft femoral marrows were all red with no fatty tissue visible. Lymph nodes found in both abdominal and thoracic cavities were all soft, less than 1.0 cm. in diameter, showing no infiltration or apparent inflammatory reaction. The brain weighed 1,230 Gm. and was grossly normal.

**Postmortem Bacteriology**


**Microscopic Findings**

The microscopic findings in this case will be presented only in so far as they are pertinent to the hematologic problem.

The spleen showed for the most part preservation of its basic architecture. There was, however, an over-all increased cellularity which somewhat obscured the follicular and sinusoidal pattern (fig. 1). The pulp was increased in amount with thickening of the sinusoidal walls. It was markedly congested with a pronounced reticulo-endothelial hyperplasia. Many large phagocytic cells were present in the pulp, containing fragments as well as intact red and white cells. Prominent foci of plasma cells, as well as scattered plasma cells, were found throughout the pulp. Hemosiderin deposits were likewise prominent.

The sinusoids were for the most part collapsed. However, some were partially dilated, showing considerable hypertrophy of the lining endothelium. Many large, some giant, phagocytic macrophages were present within these sinusoids, engulfing red cells and white cells in all stages of disintegration (figs. 2 and 3). Considerable phagocytosis was also
evident within the lining reticulo-endothelial elements. These phagocytic cells also contained considerable amounts of blood pigment. Hematopoiesis was absent. The follicles, capsule, trabeculae and blood vessels were all normal.

The liver microscopically was essentially normal. It showed preservation of its usual
Fig. 4—Liver showing hyperplasia of R-E elements and one Kupffer cell with phagocytosed polymorphonuclear leukocytes. ×980

Fig. 5—Lymph node sinus showing many phagocytic cells containing red and white cells and nuclear debris. ×560

architecture with red and white blood cells and cellular debris found within the Kupffer cells (fig. 4). No extramedullary hematopoiesis was present.

The lymph nodes showed a reticulo-endothelial hyperplasia quite analogous to that
present in the spleen. Many plasma cells were found in the pulp. Cytophagocytosis of both red and white elements was evident and abundant in the R-E cells and in the macrophages within the sinuses (fig. 5). Traces of hemosiderin were likewise present in these cells. The germinal follicles and capsule were not involved. No myelopoiesis was present in these organs.

The marrow presented a significant deviation from the normal. There was an increased cellularity with diminution of the usual number of lipid cells. There was an increased number of red cell elements showing all stages of development from primitive erythroblasts to mature nucleated red cells. Dominant in this series was the normoblastic-nucleated red cell level. The usual myeloid preponderance was replaced by a distribution in which there appeared to be an equal number of white and red cell elements. In the white cell series a complete maturation block at the metamyelocyte level was present. Very few of these cells and no mature polymorphonuclear leukocytes were present (fig. 6). The majority of the white cell elements were myelocytes with an increased number of stem cells. Occasional hypertrophied R-E cells demonstrated phagocytosis of both red and white cells.

The remainder of the microscopic findings in the postmortem were not pertinent to the present hematologic disorder, but did demonstrate a focus of adenocarcinoma in the prostate, foci of subcutaneous fat necrosis in the left upper arm, acute pyelonephritis with necrotizing papillitis, and organizing bronchopneumonia with abscess formation.

In view of the marked phagocytosis of white blood cells in this case, it is pertinent to note that no histologic features of lupus erythematosus were seen.

**DISCUSSION**

The present study is quite distinctive in that it encompasses within one case practically all of the histologic characteristics previously cited as occurring in cases of hypersplenism as well as several features heretofore undescribed. The hyperplasia and phagocytic activity of the R-E system involved not only the
spleen, but extended as well to the lymph nodes, liver and bone marrow. Such generalized changes were apparently not present in the autopsied cases reported by Price and Schoenfeld, Williams, Hirschboeck and Heinle and Holden. The marked phagocytic activity of both the free and fixed R-E cells extended to both the red and white cells and appeared to be of sufficient severity to explain a considerable depletion of both the red and white cell count in the circulating blood. Sequestration of the circulating blood cells, as emphasized by Doan, was not prominent in our case.

Of equal interest from a histologic point of view was the finding of maturation arrest of the white cell series in the bone marrow. While there appeared to be active complete maturation of the red cells, few white cells above the level of maturity of the myelocyte were found. It is of interest that a similar finding was present in the case previously reported from this laboratory by Williams.

An additional feature of considerable significance in this case was the finding of a so called leukocidin. This was a substance present in the blood serum which in the presence of complement would lyse normal white cells, in vitro. The exact nature of this substance was not elucidated, and it represents, to the best of our knowledge, the first demonstration of this phenomenon in instances of hyper-splenism.

These findings are relevant to the controversy over the mechanism by which splenic hyperfunction produces its effect. Doan and his co-workers have stressed excess sequestration and cytophagocytosis of blood cells in the splenic pulp and sinuses. The bone marrow has been reported by them to be significant only in so far as it demonstrates no failure of maturation and/or delivery. These histologic findings have been used by them to support the hypothesis that the peripheral cytopenias are due to the mechanical removal of blood elements by a hyperactive spleen. The anatomic findings of excessive phagocytic activity of the spleen and R-E system offer support to this hypothesis.

On the other hand, the finding of maturation arrest of the white cell series in the marrow confirms the opinion of Dameshek and his colleagues, who have been less impressed with the local splenic removal of blood elements. They suggest that splenic hyperfunction exerts its effects chiefly through the elaboration of a humoral substance that suppresses normal marrow function, presumably producing arrest of blood cell formation or block in the delivery of formed cells.

In his extensive study, Von Haam concluded that the histologic evidence of local phagocytosis of blood cells in the spleen was insufficient to explain adequately the peripheral blood cytopenias. He postulated the possible elaboration of a substance which would locally destroy blood cells. The demonstration of a leukocidin in this case lends some support to this hypothesis. How much effect it had in producing the depression of the white blood count can only be speculated upon. However, at the time it was demonstrated, the white blood count was considerably lower than on a subsequent day when this leukocidin had apparently disappeared from the blood stream.

Thus, while not resolving the problem, our case gives evidence to support each of the above concepts of splenic hyperfunction.

Mention should be made in passing of the possible exposure to paint solvents...
and organic materials. The clinical history of long duration without sudden onset, and the histologic findings, both argue against the significance of exogenous agents as the cause of the observed hematologic disorders.

It is known that cytophagocytosis may be seen in patients who have received many transfusions, however, in our experience, never to the extent seen in this case. Moreover, the striking phagocytosis of white cells is inconsistent with a response to transfusions alone.

The present case has all the features of the clinical syndrome described by Felty. This does not, however, help to resolve the problem of whether the splenic hyperfunction is related to the rheumatoid arthritis or coincident with it. However, the size of the spleen in this case, 780 Gm., is considerably larger than those usually associated with rheumatoid arthritis.

In considering the etiology of this syndrome, the generalized R-E activity in the present case merits further emphasis. The anatomic findings strongly suggest that hyperactivity of the entire R-E system and not the spleen alone may have been responsible for the existing cytopenias. These observations may help to explain the failure of splenectomy to effect a cure in some reported cases of hypersplenism.

SUMMARY

A case of hypersplenism giving rise to a panhematopenia is presented with complete postmortem study. Its association with rheumatoid arthritis permits it to be classified as a Felty's syndrome. There was histologic evidence to support both of the now existing concepts of the mechanism by which splenic hyperactivity effects its cytopenias. Marked phagocytosis of both red and white cells was noted in the spleen. There was, in addition, similar phagocytic activity throughout the entire R-E system. Equal support for the hypothesis that splenic hyperfunction depresses or blocks bone marrow function was adduced from the finding of a complete maturation arrest of the white cell series of the bone marrow at the myelocytic level.

A third factor, to the best of our knowledge never previously identified in cases of hypersplenism, was also present. This was a circulating substance which produced active lysis of normal white cells and must have contributed to the leukopenia.

The anatomic observations in this case raise the possibility that generalized R-E hyperfunction and not simply splenic hyperfunction may be of significance in the production of cytopenias in some of the patients with so called hypersplenism.

REFERENCES

CASE REPORT


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Case Report: Hypersplenism: A Case Report with Postmortem Study

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