Phospholipid Accumulation in Histiocytes of Splenic Pulp Associated with Thrombocytopenic Purpura

By Sidney L. Saltzstein

Accumulation of lipid, presumably phospholipid, in histiocytes of the splenic cords has been seen in association with thrombocytopenic purpura in six patients operated on in Barnes Hospital. At the time that each of the first four were examined, a diagnosis or description of lipid histiocytosis of the spleen was made, but after that the constant association with thrombocytopenic purpura was noted. Three of the cases were seen between November of 1958 and November of 1959, a fourth in September 1960, and the fifth and sixth were located by review of sections of all 737 spleens removed or biopsied in Barnes Hospital from 1922 through 1960. Five of the six patients had otherwise typical idiopathic thrombocytopenia; the sixth had amegakaryocytic thrombocytopenia.

A seventh case, similar in most respects, which was reported by Carpenter et al. has been included in this report as Case 7. These authors excluded one case from their group of cases of idiopathic thrombocytopenic purpura because it showed "... an abnormality not usually encountered in ITP; e.g., ... infiltration of the spleen by non-lipid containing macrophages." Review of the sections of the spleen in this case showed the same lesion as in our six cases, except that very little stainable lipid was found.

Case Reports

Case 1: S. N., who was 52 years of age when admitted to Barnes Hospital (service of Dr. D. Allen) in April 1953, noted easy bruising and prolonged bleeding after minor cuts since childhood. Following a tonsillectomy performed when he was in his teens he had severe bleeding. Petechiae had been present on his skin for many years. He came to the Washington University Clinics because of dysphagia which he had had for three years. A diagnosis of peptic esophagitis was made. However, a platelet level of 45,000/mm$^3$ (indirect) was found. The only medication the patient had received was vitamin K for the one episode of massive hematemesis (estimated at one pint of bright red blood) which he had one and one-half years earlier. There was no history of diabetes mellitus. He was admitted to Barnes Hospital.

Positive findings on physical examination included petechiae on the ankles, legs, flank and conjunctivae; absence of lymphadenopathy and palpable enlargement of any abdominal organs. A repeat platelet count (indirect) was 10,000/mm$^3$. The leukocytes were elevated to 15,000 mm$^3$. The bone marrow contained an abundance of megakaryocytes. Platelet agglutinins were present. No serum cholesterol level was determined.

Splenectomy was performed on April 28, 1953, without difficulty. By the end of the first post-operative day the platelet level (indirect) had risen to 195,000/mm$^3$.

One month later his platelet count was 750,000/mm$^3$. The patient died on December 25, 1953. The death certificate states that the cause of death was "coronary thrombosis." No autopsy was performed. He had no evidence of purpura in the interim.

From the Division of Surgical Pathology, Washington University Medical School, and Barnes Hospital and The Barnard Free Skin and Cancer Hospital, St. Louis, Missouri. Submitted Jan. 11, 1961; accepted for publication Apr. 27, 1961.
Case 2: Mrs. N. H., a 69 year old white housewife, entered Barnes Hospital on August 6, 1954 (service of Dr. C. M. Charles and Dr. R. Steinkamp). For four or five years, she had noted easy bruising with minor trauma, and for five months she had had spontaneous ecchymoses. A diagnosis of idiopathic thrombocytopenic purpura had been made. She was treated with cortisone with some improvement of her symptoms, but continued to have spontaneous ecchymoses. Two months before admission, she had one spontaneous mild epistaxis. She had had “dyspepsia” all her life, and 12 years previously a clinical diagnosis of “stomach ulcer” had been made. Antacids gave relief of her symptoms. A hysterectomy had been performed 25 years ago without difficulty.

She had extensive purpura on admission, especially on her extremities. No other abnormalities were noted except for a blood pressure of 170/105. Her liver and spleen were not palpable.

Laboratory data included a hemoglobin level of 13.7 Gm./100 cc., a white blood cell count of 10,200/mm³, and 2.1 per cent reticulocytes, and a platelet count (indirect) of 4,000/mm³. A bone marrow examination showed increased cellularity with increased numbers of megakaryocytes in all stages of development. No platelets or pseudopods were seen. The myeloid and erythroid series were interpreted as normal. Platelet agglutinins were present. The serum cholesterol level was not determined.

On the second hospital day, a splenectomy was performed (Dr. W. Walker). Considerable capillary oozing was encountered during the operation, but no other complications occurred, either during the operation or post-operatively.

By the fourth post-operative day, her platelet count (indirect) rose to 280,000/mm³. There was a persistent reticulocytosis ranging from 3.4 per cent to 7.4 per cent. On the seventh and ninth post-operative days, benzidine tests on her stools were positive for occult blood. The melena was attributed to a duodenal ulcer, which was demonstrated roentgenographically. Attempts to reduce the dosage of cortisone coincided with falls in the platelet counts. She was discharged on the 16th hospital day. At this time her therapeutic regimen included the use of cortisone, 25 mg./day, antacids, bland diet and ferrous gluconate. When last contacted by her personal physician on April 5, 1960, she was in good general health and able to carry on all her household duties. She had had no symptoms of thrombocytopenia since discharge and steroid therapy had been discontinued shortly thereafter.

Case 3: S. S., a 54 year old white businessman, was admitted to Barnes Hospital (service of Dr. W. Harrington) on November 22, 1958 for splenectomy for idiopathic thrombocytopenic purpura. In August of 1958 he noted a spontaneous ecchymosis on his left hip. He was found to have a platelet count of 60,000/mm³. In the next month more ecchymoses appeared. He was seen in another institution, and a platelet count of 23,000/mm³ was recorded. Therapy with adrenal cortical hormones resulted in suboptimal improvement in his platelet count and attempts at reducing the dosage of the hormone resulted in recurrence of the low platelet count. In February 1958 he had had low abdominal post-prandial pain and a duodenal ulcer was demonstrated on x-ray. The pain was relieved by antacids. There was no melena. In June 1958 an uneventful transurethral resection of the prostate had been carried out at another hospital.

Physical examination at the time of admission to Barnes Hospital was within normal limits except for one old ecchymosis over the right elbow. The liver and spleen were not felt. His hemoglobin level measured 17.7 Gm. per 100 cc., and his white blood cell count was 17,900/mm³. His platelet count was 21,000/mm³. His bone marrow contained an abundance of megakaryocytes. Platelet agglutinins were not present. No serum cholesterol determination was performed.

On the third hospital day, splenectomy and liver biopsy were performed (Dr. H. R. Butcher, Jr.) with no difficulties. A few small ecchymoses of the omentum developed during the course of the operation, but no gross bleeding occurred. ACTH therapy (25 units/day) was instituted before surgery, and the adrenal corticoid (methylprednisolone) therapy was continued. No post-operative complications developed. The platelet count rose gradually to 280,000/mm³ on the seventh post-operative day. The adrenal corticoid and
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ACTH dosage were tapered off and had been discontinued by the time he was sent home on the ninth post-operative day.

However, thrombocytopenia (21,000 platelets/mm³) recurred within a few weeks. In May 1959, six months after discharge, he developed a "rash" on his legs, and his platelet count was 45,000/mm³. Therapy with prednisone was instituted, but was discontinued after three months. In October 1959, his platelet count was 48,500/mm³, but he was asymptomatic except for a solitary ecchymosis. He has remained (January 1961) clinically well, but frequent platelet counts have varied between 20,000 and 70,000/mm³.

Case 4: Mrs. L. L., a housewife 68 years of age, had her first episode of purpura following therapy with sulfisoxazole and chloramphenicol for a lower urinary tract infection in 1955. Her platelet count at the time was 30,000/mm³, and platelet agglutinins (performed elsewhere) were demonstrated in her serum. During the next four years she had intermittent cutaneous purpura, seemingly following exposure to various chemicals or drugs. These episodes were usually relieved by steroid therapy, but as time progressed, the therapy became less effective. Splenectomy was recommended at another institution, and she was admitted to Barnes Hospital (service of Dr. C. V. Moore) on January 1, 1959 for evaluation of her hematologic status.

On admission, the physical examination was within normal limits except for the scar of a previous right simple mastectomy, performed in 1939 presumably for carcinoma. Her liver and spleen were not palpable. Laboratory data included a hemoglobin level of 12.9 Gm./10 cc. and a white blood cell count of 12,300/mm³. Her platelet count was 86,000/mm³, and there were 7.2 per cent reticulocytes in the peripheral blood. Platelet agglutinins were not demonstrated. A serum cholesterol level was 238 mg./100 cc. Prednisone, 20 mg./day, was given, and the patient was sent back to the referring institution, where a splenectomy was performed on February 12, 1959.

One week post-operatively, her platelet count had risen to 320,000/mm³. Adrenal cortical hormone therapy had to be re-instituted once since then for recurrence of thrombocytopenia, but was discontinued in September 1960. In November 1960, her platelet level was 380,000/mm³. She was without symptoms referable to any hematologic disorder when last seen in February 1961.*

Case 5: C. B., a 43 year old white man, was admitted to the ward service of Barnes Hospital on November 20, 1959 for evaluation of thrombocytopenic purpura. At 17 years of age, he had an episode of "anemia," at which time he was "not expected to survive." An appendectomy (1944) and a tonsillectomy and adenoidectomy (March 1959) were performed without hemorrhagic complications.

In August 1958 he began having arthralgias, muscle spasm, progressive weakness and easy fatigability, anorexia and weight loss. Ecchymotic and purpuric areas appeared, especially on the legs, in August 1959. In September, his hemoglobin was 37 per cent and his platelet counts decreased from 52,000 to 22,000/mm³. His white count ranged from 10,000 to 14,000/mm³ with a definite shift to the left.

A bone marrow examination in September had revealed a slight decrease in the erythroid series and a marked increase in the myeloid cells. Only one megakaryocyte was seen in several preparations. He was given prednisolone, 20 mg. per day, which was gradually increased to 160 mg. per day without significant remission of his signs or symptoms. Busulfan, 4 mg. per day was started in October, and hesperidin complex and ascorbic acid in the middle of November. These also resulted in no significant change in his clinical status.

On the admission physical examination, he exhibited the typical "Cushingoid" facies, a buffalo hump, and central obesity. Petechiae and ecchymoses were present over most of his skin and on the buccal mucosa. The liver was palpable 4 cm. below the right costal margin and the spleen 2 cm. below the left costal margin. Slight pitting edema of the ankles was noted.

*Gross description and sections of the spleen supplied through the courtesy of E. R. Halden, Jr., M.D., Department of Pathology, and D. W. Seldin, M.D., Department of Internal Medicine, Southwestern Medical School, University of Texas, Dallas, Texas.
His hemoglobin measured 10.4 Gm. and his white blood cell count was 12,150/mm.³ with a shift to the left. Only 1,000 platelets per cu.mm. were present, and there were 8.1 per cent reticulocytes. A bone marrow aspiration at this time was interpreted as showing erythroid hyperplasia, hemosiderin deposition, and a marked decrease in the number of megakaryocytes. Stools were repeatedly guaiac positive, and the admission urinalysis showed 2–3 red blood cells per high power field. Platelet agglutinins were not demonstrated. A serum cholesterol determination was not done.

Initially, the patient’s hematocrit fell from 33 per cent to 28 per cent and his stools remained guaiac positive. Prednisolone dosage was gradually reduced from 160 to 20 mg per day. The hematocrit stabilized at 30 per cent, although the stools remained guaiac positive. He was treated with antispasmodics, antacids and a bland diet with symptomatic relief. However, fresh areas of purpura were noted. The platelet count continued to drop, reaching zero on the tenth hospital day. Thereafter, it rose to between 1,000 and 4,000/mm.³

In addition to adrenal cortical hormones, infusions of plasma from thrombocytotic individuals were tried without success to raise the platelet count. Finally, splenectomy was considered to be the only remaining therapy offering some chance of success.

Splenectomy were performed on December 10, 1959 (Dr. K. Williams). Much trouble was encountered both during the operation and post-operatively from bleeding, a left hemothorax, and wound infection. Post-operatively, the platelet count ranged from 1,000 to 6,000/mm.³ The patient was discharged on December 26, 1959, against medical advice. His medications at the time included phenobarbital, dexamethasone and antacids. He died 3 days later in his home town after a terminal course of fever and gastrointestinal hemorrhage. At autopsy, widespread petechiae, hemorrhage into the gastrointestinal tract and a left hydrothorax were found. Sections of bone marrow obtained at autopsy contained only very rare megakaryocytes. There was no evidence of leukemia or lymphoma. No lipid-filled macrophages of the type seen in the spleen were found in any organs.

Case 6: In May 1960, J. K., a 12 year old white schoolgirl, noticed a fine red papular rash over her legs. Shortly thereafter, she developed purpura on her tongue. Her pediatrician found a platelet count of 34,000/mm.³ One week later the count had dropped to 16,000/mm.³ with an associated increase in the lesions and excessive menstrual flow. When she was treated with methylprednisolone, her platelet counts ranged from 40,000 to 140,000/mm.³, but she developed moon facies, hirsutism, increased acne, purple abdominal striae, and a buffalo hump, and gained 10 pounds in weight.

On admission to Barnes Hospital (service of Dr. Carl V. Moore) on September 1, 1960, features of hypercortisonism were evident. Examination of the skin revealed old purpuric lesions. The liver and the spleen were not palpable. The rest of the physical examination was within normal limits. The laboratory data on admission included a hemoglobin level of 14.3 Gm./100 cc., a red blood cell count of 5 million/mm.³, a reticulocyte count of 4.2 per cent and a white blood cell count of 12,550/mm.³ Her platelet count was 19,000/mm.³ The bone marrow was of normal cellularity with many megakaryocytes. Platelet agglutinins were not present. The remainder of the laboratory examination was unremarkable. The serum cholesterol level was not determined.

Because of the signs of hypercortisonism and the mediocre response to therapy, splenectomy was advised. It was performed on September 3, 1960 (Dr. W. Cole) without difficulty and without significant blood loss. The post-operative course was entirely without incident. The dosage of adrenal cortical hormones was gradually decreased and discontinued. Her platelet count rose to a peak of 1,500,000/mm.³ on the ninth post-operative day and dropped back to 925,000/mm.³ by the 13th post-operative day.

She was discharged on September 17, 1960, receiving no medication, and was followed on an out-patient basis. Three months later she was clinically asymptomatic, and had a platelet count of 835,000/mm.³.

*The autopsy material was supplied through the courtesy of Dr. D. G. Gorelick, Springfield, Mo.
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Case 7. G. S., a 54 year old woman, noted easy bruising for 8 years, and menometrorrhagia for 3 years before being seen at the University of Utah College of Medicine in 1956. Physical examination showed petechiae over the skin and palate and freshly clotted blood in one nostril. A tourniquet test was positive. Examination of the peripheral blood disclosed a white blood cell count of 10,000/mm³ and a hematocrit of 49 per cent. Platelet counts ranged from 9,000 to 100,000/mm³. Morphologically normal megakaryocytes were plentiful in her bone marrow. Prednisone, 40 mg./day, was given and the platelet count rose to 284,000/mm³. Two months later, splenectomy was performed. The spleen weighed 300 Gm. but was otherwise grossly unremarkable.

Since splenectomy, the patient has required 10-20 mg. of prednisone daily to maintain her platelet count at or near normal. On the two occasions when steroid therapy was stopped, her platelet count fell. She has been clinically asymptomatic.

Gross Appearance

The weights of the spleens varied from 62 Gm. to 465 Gm. (table 1). Externally and on section, the organs presented no abnormalities, except that in Case 5, a 2 mm. calcified nodule was noted. Two accessory spleens, 3 mm. and 5 mm. in diameter, were also found in this man.

Microscopic Appearance

The microscopic appearances of the spleens were quite similar, differing only in the extent of involvement. Large cells, apparently histiocytic in nature, were scattered throughout the red pulp. The nuclei of these cells were round to oval, often eccentric, and each had a single, fairly prominent nucleolus (figs. 2, 4, 8). The cells had abundant foamy cytoplasm, and indistinct cell borders (figs. 2, 4, 8). These cells frequently bulged into, but did not actually line, the sinusoids (fig. 4) and tended to be concentrated about the Malpighian corpuscles (figs. 1, 5, 7, 10). The material within the cells stained readily with various fat stains (Oil Red-O, Sudan Black B, Scarlet Red) (figs. 3, 6). The amount of stainable lipid varied from case to case, and with the particular fat stain used. In Case 7, almost no lipid was stained in the sections prepared at the University of Utah. The periodic acid-Schiff method faintly stained rare particles within these cells. Baker's acid-hematin stain was strongly positive in the two cases in which fresh material was available (fig. 9). Tissue extracted with pyridine before staining did not take up this stain. In Case 5, similar changes were present in two accessory spleens (fig. 8). Otherwise, the spleens presented no unusual microscopic features. There was no evidence of hemolysis in the form of erythrophagocytosis or hemosiderin deposition. In Case 5, an incidental fibrotic granuloma was found in which the yeast form of Histoplasma capsulatum was stained by the Gomori methenamine silver nitrate technique.

In the one case (3) in which the liver was also biopsied, the only microscopic change was a diffuse, marked fatty change. Splenic hilar lymph nodes were unremarkable in the instances they were resected and sectioned.

*This case has been reported by Carpenter et al. A clinical abstract was supplied through the courtesy of Dr. A. F. Carpenter, and the sections by Dr. H. E. Butler, University of Utah College of Medicine, Salt Lake City, Utah.
Table 1.—Clinical Summary

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>Duration of symptoms</th>
<th>Lowest platelet count</th>
<th>Platelet agglutinins</th>
<th>Steroid therapy</th>
<th>Peptic ulcer and/or G.I. bleeding</th>
<th>Weight of spleen</th>
<th>Interval</th>
<th>Platelet count</th>
<th>Steroid therapy needed</th>
<th>Symptoms persist</th>
</tr>
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<tbody>
<tr>
<td>1. 52WM</td>
<td>80</td>
<td>M</td>
<td>78</td>
<td>Since childhood</td>
<td>10,000</td>
<td>pos.</td>
<td>no</td>
<td>yes (prior to steroid Rx)</td>
<td>65 Gm.</td>
<td>1 mo.</td>
<td>750,000</td>
<td>no</td>
<td>no</td>
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<tr>
<td>2. 69WF</td>
<td>4–5 yrs.</td>
<td>F</td>
<td>4,230</td>
<td>pos.</td>
<td>yes</td>
<td>slight</td>
<td>yes</td>
<td>110 Gm.</td>
<td>165,000</td>
<td>1 mo.</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>3. 54WM</td>
<td>3 mos.</td>
<td>M</td>
<td>21,000</td>
<td>neg.</td>
<td>yes</td>
<td>good</td>
<td>yes (prior to steroid Rx)</td>
<td>62 Gm.</td>
<td>3 yrs.</td>
<td>70,000</td>
<td>no</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>4. 68WF</td>
<td>4 yrs.</td>
<td>F</td>
<td>30,000</td>
<td>neg.</td>
<td>yes</td>
<td>good</td>
<td>no</td>
<td>250 Gm.</td>
<td>22 mos.</td>
<td>3 mos.</td>
<td>380,000</td>
<td>no</td>
<td>none</td>
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<td>5. 43WM</td>
<td>15 mos.</td>
<td>M</td>
<td>zero</td>
<td>neg.</td>
<td>yes</td>
<td>none</td>
<td>yes (after steroid Rx)</td>
<td>465 Gm.</td>
<td>2 wks.</td>
<td>6,000</td>
<td>yes</td>
<td>died</td>
<td></td>
</tr>
<tr>
<td>6. 12WF</td>
<td>4 mos.</td>
<td>F</td>
<td>16,000</td>
<td>neg.</td>
<td>yes</td>
<td>good</td>
<td>no</td>
<td>187 Gm.</td>
<td>3 mos.</td>
<td>3 yrs.</td>
<td>835,000</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>7. 54WF</td>
<td>8 yrs.</td>
<td>M</td>
<td>9,000</td>
<td>—</td>
<td>yes</td>
<td>good</td>
<td>—</td>
<td>300 Gm.</td>
<td>3 yrs.</td>
<td>230,000</td>
<td>74,000</td>
<td>yes</td>
<td>no</td>
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</table>

*Attributed to "coronary thrombosis" on death certificate.
†Patient requires lower dosage of steroids.
Fig. 1.—Case 1. Concentration of lipid-filled macrophages in splenic white pulp immediately around Malpighian corpuscles. H & E. x275 (W.U. Ill. #60-7928A).

Fig. 2.—Case 2. Large, lipid-filled macrophages in splenic white pulp. H & E. x620 (W.U. Ill. #60-4380).

Discussion

These seven patients showed the variety of clinical features which might have been expected in any group with thrombocytopenia (table 1). Six of the seven were adults and the other an adolescent. The lowest pre-operative plate-
let counts ranged from zero to 30,000/mm$^3$. Five of the six who received steroid therapy pre-operatively responded with elevations of their platelet counts. In two (1 and 2) of the Barnes Hospital patients, platelet agglutinins were demonstrated. Three patients developed signs and symptoms of duodenal ulcers, one (5) while on steroid therapy, and two (2 and 3) before steroid
therapy was instituted. The man who received no steroids (1) had symptoms which clinically were thought to be peptic esophagitis. Only Case 5 received blood transfusions before operation.

One patient (5) did not respond to splenectomy. A second (7) required continued steroid therapy to maintain the platelet count at or near normal
values. In another case (3), there was continued thrombocytopenia following splenectomy. In the other four cases (1, 2, 4, and 6), clinical and hematologic remissions were obtained after splenectomy, although in one of these cases, a temporary relapse in thrombocytopenia occurred, requiring resumption of
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Fig. 9.—Case 5. Phospholipid present in large, lipid-filled macrophages of spleen. Baker's acid hematin x220 (W.U. Ill. #60-5672).

Fig. 10.—Case 6. Concentration of lipid-filled macrophages in splenic white pulp immediately around Malpighian corpuscles. H & E. x110 (W.U. Ill. #60-6015).

steroid therapy. This group of seven patients is too small to allow any conclusion as to the effects of splenectomy.

All except Case 5 had idiopathic thrombocytopenic purpura. He differed slightly from the others. This man had the lowest pre-operative platelet
count (zero), did not respond to massive steroid therapy pre-operatively or to splenectomy, and died of hemorrhage three weeks post-operatively. His bone marrow showed only a rare megakaryocyte (in contrast to the normal or increased number in the other cases) and for this reason the anatomic diagnosis of "amegakaryocytic thrombocytopenic purpura" was made.

Grossly, the spleens were without striking or diagnostic characteristics. The average weight was 206 Gm., and only one (Case 5) weighed more than 300 Gm. In no instance was anything abnormal other than the inconstant, slight splenomegaly noted either on external examination or on section.

The microscopic characteristics of these seven spleens resembled those of Gaucher's Disease and Niemann-Pick's Disease only superficially. The lipid-filled macrophages associated with thrombocytopenic purpura were not as large or as numerous as those in the latter two diseases, nor did they have the laminated cytoplasm of Gaucher's cells or the marked foamy appearance or very large size of Niemann-Pick's cells. Lipid-filled cells were not found in the bone marrow of any of these cases, and the clinical features were distinctively different from Gaucher's Disease and Niemann-Pick's Disease.

Deposition of lipid material in large macrophages of enlarged spleens has been described in association with diabetes mellitus and hyperlipemia. None of the seven patients in this report had diabetes or were known to be hyperlipemic. The foamy macrophages in thrombocytopenic purpura were perifollicular in distribution, while those of hyperlipemia tended to be more diffuse (fig. 11).

Fig. 11.—Diabetic Hyperlipemia. Fifty-seven year old woman with mild diabetes who eventually developed a serum cholesterol of 1180 mg./100 cc. Total serum lipids four times normal. Platelet count normal. The lipid-filled macrophages are very numerous, and clustered diffusely throughout the entire spleen without any perifollicular pattern. H & E. x135 (W.U. Ill. #80-7927A).
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Fig. 12.—"Follicular" or "mineral oil" lipoidosis of the spleen. The fat vacuoles are large, located in the Malpighian corpuscles, and have elicited a foreign body reaction. H & E. x310 (W.U. Ill. #60-7929A).

Lipid deposits in the spleen, characterized by large, clear cells within the Malpighian bodies, and usually accompanied by chronic inflammation with giant cells (fig. 12) have been found in patients and animals who have received large amounts of liquid petrolatum. None of these histologic features were present in our cases.

Scattered foamy macrophages have been described in the spleen in children with thalassemia. None of these seven cases had thalassemia, and with the possible exception of Case 5, none had splenomegaly which is associated with thalassemia. Also, the foamy macrophages associated with thrombocytopenic purpura were more numerous than those reported in thalassemia.

Large histiocytes or reticular cells, not foamy in nature, which bulged into the splenic sinuses have been described previously in association with idiopathic thrombocytopenic purpura. Marshall and Adams have reported a single case which had a striking similarity to ours. A 61 year old man with a 30 year history of purpura had a pre-operative platelet count of 30,000/mm. Total serum lipids were slightly elevated, but serum cholesterol and lipoprotein levels were normal. After splenectomy, the platelet count rose to 300,000/mm. The spleen weighed 730 Gm. and contained numerous dark red nodules. Microscopically, the nodules were angiomatous and in the pulp between the nodules there was a diffuse infiltration of macrophages with coarsely to finely vacuolated cytoplasm. Combining histochemical and chemical determinations, these authors concluded that the material in these macrophages contained phospholipid and glycolipid. We have seen two cases of hemangiosarcoma of the spleen associated with thrombocytopenia, and Videbaek has reported the association of hypersplenism with hamartomas of the spleen.
During the review of the sections of the 737 spleens in our files, only two findings caused any confusion with the lipid deposits associated with thrombocytopenic purpura. One was the “mineral oil” or “follicular” lipidosis described above. The characteristics of the fat cells, the surrounding reaction, and the intra-follicular location allows an easy differentiation of this entity from the lesions associated with thrombocytopenic purpura. The second source of confusion resulted from the indistinct boundaries in thin sections of the reticuloendothelial cells, which, associated with small portions of red blood cells and precipitated plasma in the sinusoids, gave the appearance of foamy macrophages. This effect was most noticeable in tissue fixed in Zenker’s solution. Careful study of these areas, and comparison with thicker portions of the section, could properly identify the artefact.

The material within the foamy macrophages was assumed to be a phospholipid. It did not have the appearance of cholesterol, and in the one patient on whom a serum cholesterol determination was performed, it was normal. The lipid could be stained with the usual fat stains. In the fifth and sixth cases, it stained intensely with Baker’s acid hematin stain, and did not stain after pyridine extraction. This combination of reactions has been considered specific for phospholipids. Fat stains performed on paraffin-embedded material were negative, as were acid-fast stains, excluding ceroid as the lipid. Some carbohydrate may have been present, as the PAS stain was faintly positive.

Platelet phagocytosis conceivably could have been a source of phospholipid, although platelets were not seen in the foamy macrophages. Human platelets have been shown to have a high proportion of the total lipid present as phospholipid, and carbohydrate also has been demonstrated in platelets. Although small amounts of phospholipid have been detected in erythrocytes, they would have been an unlikely source of the foamy material in the macrophages in the absence of clinical evidence of hemolysis or unexplained anemia and of pathologic evidence of iron deposition. Considerable phospholipid has been demonstrated in leukocytes; all seven patients had normal to elevated white blood cell counts. Finally, sources of lipid other than the formed elements of the blood, or formation of lipid in situ in the cells also could have accounted for the foamy histiocytes.

It is interesting that all seven of these cases have occurred since 1953. Review of the sections of all 737 spleens removed or biopsied in this institution from 1912 through 1960 disclosed no cases of this type of splenic lipoidosis other than the ones reported. Included in these 737 spleens were 137 removed for idiopathic thrombocytopenic purpura (79 before 1953, 58 in 1953 or later), as well as many removed or biopsied for other hematologic disorders, splenic tumors and cysts, traumatic rupture, and extra-splenic diseases (in the course of spleno-renal shunts and radical cancer operations). Similarly, Carpenter et al. found no example of this lesion, other than Case 7, in a thorough review of splenic histology in idiopathic thrombocytopenic purpura. Although the time period since 1953 corresponds generally with the increasing use of steroid therapy, the first case had received no medication other than vitamin K prior to surgery. Thus it can be assumed that if steroid therapy was causally related to the lipid accumulation in any of these cases, it did not cause it in all.
LIPID ACCUMULATION IN THROMBOCYTOPENIC PURPURA

Summary

Accumulation of a lipid, histochemically a phospholipid, in the histiocytes of the splenic pulp was observed in seven patients with thrombocytopenic purpura. Six had classical idiopathic thrombocytopenic purpura with abundant megakaryocytes in the bone marrow. Splenectomy resulted in clinical and hematologic remissions in four of these six, continued thrombocytopenia in the fifth, and in the continued requirement of corticosteroid to maintain a reasonably normal platelet count in the sixth. The seventh patient, who died shortly after splenectomy, had marked hypoplasia of megakaryocytes. Similar lipid accumulation was not seen in more than 700 other spleens, removed for a variety of reasons, reviewed in this study. Platelet phagocytosis has been suggested as a source of the lipid.

Summario in Interlingua

Accumulation de un lipid—histochimicamente un phospholipido—esseva observate in le histiocytos de pulpa splenic in septe patientes con purpura thrombocytopenic. Sex habeva classic idiopathic purpura thrombocytopenic con abundant megacaryocytos in le medulla ossee. Splenectomia resultava in remissione clinic e hematologic in quatro de ille sex, in continuate thrombocytopenia in le quinte, e in le continuante requerimento de corticosteroid pro mantener un plus o minus normal numeracion plachettal in le sexte. Le septime patiente, qui moriva brevemente post le effectuation de splenectomia, habeva marcate hypoplasia de megacaryocytos. Simile formas de accumulation de lipid non esseva vidite in plus que 700 altere splenes que habeva essite excidite pro varie rationes le quales es revistate in iste studio. Phagocytose de plachettas es proponite como fonte del lipid.

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References

9. Saltzstein, S. L., and van Ravenswaay, T.: Hypersplenism associated with
hemangiosarcoma of the spleen. In preparation.

12. —: Personal communication.

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Phospholipid Accumulation in Histiocytes of Splenic Pulp Associated with Thrombocytopenic Purpura

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