An Unidentified Reticuloendothelial Cell in Bone Marrow and Spleen

Report of Two Cases with Histochemical Studies

By ARTHUR SAWITSKY, GEORGE A. HYMAN and JULIAN B. HYMAN

THE FINDING by two independent workers in separate institutions of an unusual type of large blue cell in the bone marrow of two patients, led to a detailed study of these cases. A review of the literature disclosed that no comparable cell had been mentioned previously in bone marrow studies although Möschlin1 described a similar cell in splenic puncture as "eine so genannt blau-pigment makrophage." Later,2 however, he stated that he had more recently seen a marrow film in which identical cells were observed.

Both patients reported here were young adults who showed a relative paucity of symptoms in association with an appreciable enlargement of liver and spleen. The routine hematologic findings in both patients were normal. Both patients have remained in good health during a follow-up period of three and a half years.

CASE REPORTS

Case 1

S. D., a 34 year old Puerto Rican housewife, was seen in the Vanderbilt Clinic of the Presbyterian Hospital, New York, in February 1946. The patient complained of watery diarrhea. This had occurred once or twice a year since the age of 12, continued over a two or three day period and consisted of three to four stools daily. These symptoms were occasionally associated with nausea and vomiting. The patient had left San Juan one year before. Physical examination disclosed a smooth, firm, 5 cm. enlargement of the liver and 3 cm. enlargement of the spleen. There was no lymphadenopathy. The diarrhea subsided on symptomatic therapy but the patient was subsequently admitted to Presbyterian Hospital in August 1946, after three days of nausea and vomiting without diarrhea. Physical examination again revealed the hepatosplenomegaly previously described. The laboratory findings are summarized in table 1. Sigmoidoscopic examination disclosed no mucosal ulcerations and biopsy of the rectal ampulla was negative for schistosomes. A direct Schistosoma mansoni skin test was immediately positive on one occasion but negative on a repeat test. The Mantoux test was negative at 1:1000 and the Mazzini test was negative. Six stools were negative for ova and parasites. The nausea and vomiting disappeared shortly. Although no amebae were ever found, the patient received a ten day course of emetine and anayoidin and was discharged asymptomatic.

The patient was essentially well except for three day episodes of diarrhea in March 1947 and July 1948, and two mild episodes of vomiting in December 1947 and August 1949, which required no treatment. Her only new complaint was related to the appearance of spontaneous ecchymoses on the arms and legs for a two week period in November 1948. Platelet count was 150,000 per c.mm. (normal 200,000 to 300,000), red and white cell counts...
were normal (see table 1), as were the bleeding and clotting times. The tendency toward spontaneous bruising continued.

She was readmitted to Presbyterian Hospital on May 4, 1950, for re-evaluation. The only additional finding on physical examination was that of chronic cystic mastitis. The laboratory findings are summarized in table 1. A study of the films obtained by repeated bone marrow aspirations revealed two abnormal cell types, similar to those of case 2 (fig. 1) described below. The other formed elements of the marrow were normal as listed in table 2.

In November 1953, a liver aspiration biopsy revealed normal liver parenchyma. None of the above cell types could be found after careful study. A marrow aspirate was found to be unchanged from that reported previously. The patient has now been followed for four years, is working full time and has no complaints other than a tendency to bruise easily.

Case 2

J. A., a 26 year old white Italian male, was admitted to Queens General Hospital in May 1949, for pulmonary tuberculosis. The past history was not significant. The patient was well until 1941, when a routine preinduction Army chest film showed an infiltrative process in the right upper lobe. A repeat x-ray revealed further infiltration following a short period of bed rest. The patient was hospitalized at Otisville Sanitorium for nine months and then discharged. About six months later, a repeat film disclosed a further increase in the infiltrative process and the patient was readmitted to Otisville. During all this time, no coughing, hemoptysis, chills, fever, anorexia, or loss of weight were experienced. Bacteriologic studies of sputa and gastric washings were always negative for acid fast organisms. In 1946, the patient was discharged against advice.

The physical findings on admission were those of a well developed, well nourished, white male in no distress and not appearing ill. There were bilateral ptterygia and pingueculae, the mouth was normal, there were palpable small nontender posterior cervical lymph nodes. Minimal bilateral axillary adenopathy was noted. The lungs were clear to percussion and auscultation. The heart was entirely normal. The abdomen was soft and nontender but the liver was enlarged to 5 cm. below the costal margin and was smooth and nontender.

The spleen was palpable 8 cm. below the costal margin and was smooth and nontender.

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**Table 1.** Laboratory Findings

<table>
<thead>
<tr>
<th>Year</th>
<th>Hb. (Gm. %)</th>
<th>WBC/ cu.mm.</th>
<th>Neut. (%)</th>
<th>Eos. (%)</th>
<th>Lymphs &amp; monos. (%)</th>
<th>Ceph. Soc. 48 hrs.</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946</td>
<td>14.2</td>
<td>7400</td>
<td>74</td>
<td>4</td>
<td>22</td>
<td>4 plus</td>
<td></td>
</tr>
<tr>
<td>1947</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 plus</td>
<td></td>
</tr>
<tr>
<td>1948</td>
<td>12.7</td>
<td>6900</td>
<td>67</td>
<td>2</td>
<td>31</td>
<td>2 plus</td>
<td>Platelets—150,000; Bleed. time —20&quot;; Coag. time—5'15&quot;</td>
</tr>
<tr>
<td>1949</td>
<td>13.6</td>
<td>8800</td>
<td>67</td>
<td>2</td>
<td>31</td>
<td>3 plus</td>
<td>A/G = 5.0/3.8 Gm. %</td>
</tr>
<tr>
<td>1950</td>
<td>14.5</td>
<td>8000</td>
<td>76</td>
<td>1</td>
<td>23</td>
<td>2 plus</td>
<td>Prothrombin time = 13 sec.</td>
</tr>
<tr>
<td>1953</td>
<td>13.8</td>
<td>8400</td>
<td>57</td>
<td>1</td>
<td>42</td>
<td>3 plus</td>
<td>Platelets—190,000; Prothrombin time = 16 sec.</td>
</tr>
</tbody>
</table>

**Patient: J. A. (Case 2)**

1949 | 13.5       | 8600       | 80        | 0        | 20                   | 1 plus         | Platelets—175,000; Bleeding time—2'; Coag. time—10'; Prothrombin—15"; A/G = 5.1/3.0 Gm. % |
The extremities were normal. Chest x-ray revealed an infiltrative lesion in the post apical area of the right upper lobe. A flat plate of the abdomen showed only hepatosplenomegaly. The Mantoux test was positive at 1:1000 but repeated sputum cultures and gastric washings were always negative for acid-fast bacilli. The Mazzini test was negative. Routine determinations of the blood chemistry were normal. The blood calcium, phosphorus, and alkaline phosphatase were also normal. Repeated sedimentation rates were normal. The remaining laboratory data is summarized in Table 1.

Lymph node biopsy disclosed a productive and hyperplastic lesion with central caseation (fig. 4). Sarcoid-like arrangement was noted. Repeated examination of the bone marrow

**Table 2.—Bone Marrow Aspiration**

<table>
<thead>
<tr>
<th></th>
<th>Patient S. D.</th>
<th>Patient J. A.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sternum May '50</td>
<td>Sternum June '50</td>
</tr>
<tr>
<td><strong>(Percent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blasts</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Neutro. myelocytes</td>
<td>19.0</td>
<td>17.0</td>
</tr>
<tr>
<td>non-segmented</td>
<td>25.0</td>
<td>34.0</td>
</tr>
<tr>
<td>segmented</td>
<td>20.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>11.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Reticulum cells</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Erythroid elements</td>
<td>18.0</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Cellularity</strong></td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Megakaryocytes</strong></td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>
from sternum and ilium with Wright stain (fig. 2) showed a hyperplastic marrow. The formed elements were in normal proportion and among these elements were many large reticuloendothelial-like cells packed with blue staining pigmented granules and another type of reticuloendothelial cell with a foamy cytoplasm, both of which are described below.

Splenic puncture, using the Silverman biopsy needle technic, revealed an abundance of the blue-pigmented reticuloendothelial cells similar to those seen in the marrow smears (fig. 3).

The clinical course in the hospital was entirely uneventful and the patient was discharged to the out-patient department. For the past three years, the patient’s general condition has remained good, and no new symptoms or findings have appeared.

Methods of Study

Morphology

Two abnormal cell types were noted in the bone marrow stained with Wright’s stain:

1. A large reticuloendothelial-like cell with a single nucleus usually ecce-
trically placed. The nuclear chromatin arrangement resembled that of reticuloendothelial cells but fine nuclear detail was obscured by the superimposed cytoplasmic granules. One or more nucleoli were frequently observed. The cytoplasm was packed with blue-staining pigmented granules of variable sizes and shapes whose stain intensity varied from a very light azure blue to a deep sea blue (figs. 1, 2, 3).

2. A large, foamy reticuloendothelial cell with scattered dark granules. Unlike the first cell described, this appeared to be a macrophage of the type not uncommonly noted in the bone marrow.

**Histochemistry**

Films of bone marrow particles and aspirate were used for the histochemical studies. The following reactions were obtained:

1. Smears stained utilizing the periodic acid Schiff reaction resulted in a pinkish homogeneous staining of the cytoplasmic granules of the large unidentified cells. The nuclei stained a very pale pink color. This reaction was consistent with the presence of mucopolysaccharides in the granules.

2. Smears exposed to diastase before staining with periodic acid Schiff techniques revealed no change in the staining capacity of the granules. This observation would indicate that the cytoplasmic inclusions were not glycogen.

3. Toluidine blue did not stain the cytoplasm. The nuclear chromatin stained a pale blue. The failure of any reaction to occur by this technic in the cytoplasmic granules suggested the absence of nucleoprotein material.
FIG. 4. Lymph node biopsy, case 2: hematoxylin and eosin. Lymph node showing a border of cells similar to those noted in spleen. Central caseation is present. Wright stain was not made and repeat sections were not obtainable.

4. Bone marrow smears prepared by a modification of the Gomori method were negative for visualization of alkaline phosphatase.

5. Use of acetic-carbol-sudan III failed to stain these cells which made it unlikely that neutral fats or fatty acids were present.

6. This absence of deoxyribose nucleic acid was suggested by the results noted with smears stained by a modification of the Feulgen technic. In this experiment, nuclear material was stained, but no staining of the cytoplasm or cytoplasmic granules was noted.

7. Thick smears of bone marrow aspirate placed into distilled water then air-dried and stained with Wright technics showed that the granules were not water soluble.

8. The usual iron staining technics did not disclose the presence of iron in any of the cells in question.

DISCUSSION

The many similarities present in the two cases such as asymptomatic hepatosplenomegaly, normal hematologic findings, and benign course indicate a possible related syndrome. Furthermore, they resemble the case Möschlin described. He reported the presence of similar blue pigmented macrophages in the spleen of a young adult male with unexplained splenomegaly. He has since noted the occurrence of these cells in a marrow film obtained from a patient with "suspected chronic malaria."

In an attempt to determine the nature of these granules, histochemical studies were undertaken. Interpretation of histochemical findings has many pitfalls.
TABLE 3.—Comparison of Tissue Mast Cells with Authors’ Cells

<table>
<thead>
<tr>
<th></th>
<th>Mast cells</th>
<th>Authors’ cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Cytoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wright's stain</td>
<td>Intense violet blue</td>
<td>Sea blue to blue green</td>
</tr>
<tr>
<td>Cytoplasmic membrane</td>
<td>Not definite</td>
<td>Not definite</td>
</tr>
<tr>
<td>Shape of granules</td>
<td>Uniformly round</td>
<td>Varied</td>
</tr>
<tr>
<td>Size of granules</td>
<td>Uniform</td>
<td>Small to large</td>
</tr>
<tr>
<td>Stained with toluidine blue</td>
<td>Deep blue</td>
<td>Unstained</td>
</tr>
<tr>
<td>B. Nucleus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Round or oval central or eccentric</td>
<td>Same</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>None</td>
<td>Frequent</td>
</tr>
<tr>
<td>C. Marrow cellularity</td>
<td>Usually hypoplastic</td>
<td>Normally active</td>
</tr>
</tbody>
</table>

However, in both cases studied above, the granules seem identical and appear to contain mucopolysaccharides.

In case 2, both the bone marrow and the splenic aspiration revealed marked infiltration by the cell type in question. This raised the possibility of the wide distribution of this cell throughout the reticuloendothelial system. It is our opinion that these cells differ from any previously described reticuloendothelial cell, macrophage, or mast cell. After reviewing our slides, Möschlin stated that he believed them to be similar to those he had previously seen in splenic aspirates.

Because certain similarities to the mast cell might be postulated, table 3 is included for comparison. The table shows that the laboratory findings differ between the two types of cells. There is also a marked difference in the clinical pictures of the patients concerned. The patients Fadem studied usually had grave prognoses, whereas our cases were practically symptom-free individuals. Both of our patients have now been followed for three and a half years and are clinically well.

From the morphologic appearance of the abnormal cell, a reticuloendothelial origin seems indicated. Since observing these two cases, we have searched for such cells in many bone marrow aspirates. Occasionally, this examination revealed the presence of reticuloendothelial cells with morphologically similar granules. The latter cells have shown sparse granularity but present similar staining properties when examined with Wright’s stain. These patients were found to have no primary hematologic disorder and usually no common clinical syndrome. It is of interest that our first patient was suspected of having schistosomiasis while the second had tissue evidence of a “granulomatous” reaction in a cervical lymph node biopsy. Thus, no common underlying disease has been revealed to date, although both our patients are suspected of having a chronic granulomatous process.

The father and sister of the patient in case 2 were examined. Bone marrow aspirations and complete physical examinations of these subjects were normal.

We are unable to postulate the function or significance of these cells at this
time. We hope that other investigators may compare their findings with those
described above and help clarify the frequency and meaning of the cell described
and its possible relationship to a syndrome including obscure hepatosplenomegaly.

Summary

1. A cell is described in the bone marrow aspirates of two patients which has
not previously been fully described. This is a large reticuloendothelial-like cell
filled with blue-staining granules. This cell has been found in successive bone
marrow films aspirated from sternum and iliac crest.

2. These cells were also found in a splenic aspiration from one of the patients
and were compared to similar cells from a case summarized by Möschlin.

3. The case reports show striking clinical similarities in the two patients, i.e.
hepatosplenomegaly in relatively symptom-free individuals. This suggests that
a common syndrome is present.

4. Differential histochemical studies of the granular material in the cytoplasm
are reported.

5. The significance and function of these unusual cells in the marrow is un-
known.

Summario in Interlingua

(1) Es describite un typo de cellula que previemente non esseva reportate
in detahio. Illo esseva trovate in aspiratos osseo-medullar de duo differente
patientes. Illo es un grande cellula de apparentia reticuloendothelial e plenate
de granulos que prende colorantes blau. Iste typo de cellula esseva trovate in
successive frottis de medulla ossea aspirate ab le sterno e le cresta iliac.

(2) Specimens del mesme typo de cellula esseva etiam trovate in un aspira-
tion splenie ab un del patientes. Illos esseva comparate con simile cellulas trovate
in un caso summarisate per Möschlin.

(3) Le reportos de nostre duo casos exhibi frappante similaritatem clinic.
In ambes hepatosplenomegalia es presente durante que alteremente le individuos
es relativamente libre de symptomas. Isto suggere que il se tracta de un syn-
drome commun.

(4) Es reportate studios histochimic differential del materia granular in le
cytoplasma.

(5) Le signification e le function de iste cellulas inusual in le medulla non es
cognoscite.

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