BONE MARROW FIBROSIS DEVELOPING IN ALEUKEMIC MYELOSIS

By H. E. TAYLOR, M.D. AND W. W. SIMPSON, M.D.

MARROW fibrosis is a disease entity characterized by fibrous tissue replacement of the bone marrow with or without varying degrees of bony sclerosis; there is an associated leuko-erythroblastic anemia and usually hepatosplenomegaly is prominent, due to extramedullary hematopoiesis in which megakaryocytes are frequently numerous.

This condition presents an intriguing problem in etiology and pathogenesis. Although the vast majority of such cases are related to neoplastic involvement of bone, not infrequently the pathologist is confronted with a case showing diffuse replacement of the cellular marrow with fibrous tissue and varying degrees of bony sclerosis for which it is difficult to suggest an adequate etiology. Such cases have been described by a number of authors, while reviews of the subject have been reported recently by Heller et al. and by Erf and Herbut.

As yet, there is no unanimity regarding the pathogenesis of this condition and as a result the literature contains a bewildering assortment of titles apparently relating to the same subject. Heller, in his exhaustive review, has attempted to clarify this chaos by suggesting that the vast majority of such cases are in all likelihood examples of atypical granulocytic leukemia in which the marrow may show varying degrees of fibrosis, and consequently he designates such cases as aleukemic myelosis. This theory is supported by several previous authors; for instance, Mettier and Rusk and Hewer correlate the marrow fibrosis with the "irritative" effect of a previously hyperplastic marrow leading to stimulation of fibrous tissue proliferation. Similarly, Hirsch reported a known case of polycythemia vera followed for thirty-one years which terminated with bony sclerosis, while Hynes discussed the clinical similarity of aleukemic myelosis and myelosclerosis, either of which may show a blood picture of leuko-erythroblastic type, with extramedullary hematopoiesis which has variously been interpreted as representing either leukemic infiltration or metaplasia associated with the marrow replacement.

Other authors, for instance, Donhauser, have indicated that marrow fibrosis may be due to the action of toxins or chronic inflammatory change, and because of this marrow replacement it was suggested that the potential hematopoietic organs revert to blood formation by a process of metaplasia with the formation of foci of extramedullary hematopoiesis. In this connection, Gall has reported bizarre extramedullary hematopoiesis in a case of benzene poisoning with fibrosis of the marrow, while Firket and Campos have produced myeloid formation with marked megakaryocytic reaction in the liver and spleen of rabbits by the use of saponin. Others have reported upon the experimental relation of marrow fibrosis to estrogenic hormones and even specific antibodies, while Vaughan has ex-
pressed the belief that some as yet unknown stimulus may lead to both the leukoerythroblastic anemia and the marrow fibrosis; the latter author has pointed out that all the cells involved, osteoblasts, fibroblasts, hemocytoblasts and megakaryocytes, arise from the primitive mesenchymal cells of Maximow.

It thus appears that not only aleukemic myelosis but certain other stimuli may lead to fibrosis of the marrow cavities. Recently we have had the unique opportunity of following the development of marrow fibrosis through its various phases in a case eventually diagnosed as aleukemic myelosis which appears worthy of record.

CASE REPORT

The patient, a male, 61 years of age, was noted to have a yellowish tinge to the sclerae following operation for hernia repair. He was admitted to the hospital for investigation on April 9, 1947. At this time he had no particular complaints. Past history, family history and routine functional inquiry were negative. Examination disclosed a mild icterus of sclerae and a palpable liver and spleen. The former was just palpable while the latter extended two fingerbreadths below the left costal margin. Otherwise, physical examination was unremarkable. Laboratory investigation revealed the following: Hemoglobin 53 per cent (7.8 Gm.), R.B.C. 3,490 million, W.B.C. 8,000 with a normal differential of neutrophils 69, lymphocytes 2.6, eosinophils 1.0, blood sedimentation rate 2.5 mm. in one hour (Westergren), hematocrit 26, MCV 76 cu. microns, MCH 21, MCHC 30 per cent, reticulocyte count 3.0 per cent, R.B.C. fragility within normal limits, blood clotting time 6 minutes, bleeding time 3.5 minutes, prothrombin activity 85 per cent of normal (Quick's method), serum bilirubin 1.35 mg. per cent, cephalin cholesterol flocculation plus two, urobiligen in urine positive 1/75, routine urinalysis negative, blood Kahn reaction negative. A glucose tolerance test showed a high blood sugar level at the one to two hour period (256 mg. and 211 mg.) but returned to normal (103 mg.) in three hours. Aspiration biopsy of liver on April 29, 1947, showed diffuse brownish pigment granules in the hepatic cells of all parts of the liver lobules. These gave a positive iron reaction. A few small foci of cells were noted in the sinusoids but the significance of these were not realized until the sections were reviewed at a later date, when it was suggested that they represented minute foci of hematopoiesis. On April 23, 1947, a sternal marrow aspiration was reported as normal. All cell types were within normal limits and the granulocyte-erythroid ratio was 3 to 1 (see table 1).
Skin biopsy and staining for iron failed to show any hemosiderosis. No definite diagnosis was made at this time, although hemochromatosis was suspected. After a series of blood transfusions the patient's hemoglobin was raised to 80 per cent and he was allowed to go home with orders to report at a later date for re-examination.

He was readmitted to the hospital in November 1947, by which time he had lost considerable weight and was complaining of fatigue. There was now a smoky color to the skin. Hemoglobin had fallen to 40 per cent (15.9 Gm.) with R.B.C. of 1,47 millions. W.B.C. was 6,150 with a normal differential count. Serum bilirubin was 0.8 mg. per cent, blood N.P.N. 41 mg. per cent and fasting blood sugar 99 mg. per cent. The urine was negative for bile but showed a positive urobilinogen 1/40. Prothrombin activity was now 48 per cent of normal and cephalin cholesterol flocculation was four plus. The total serum proteins were 6.05 Gm. with albumin 3.36 and globulin 2.69. Repeated examinations of feces for occult blood proved negative, as they had during the former admission.

During the next two months the patient remained in the hospital and his condition was slowly improved with a series of blood transfusions. Blood smear on January 23, 1948, gave the first evidence of immature cells in the peripheral blood. At this time, hemoglobin was 54 per cent, R.B.C. 3.3 million per cu. mm., W.B.C. 6,900 per cu. mm. with 1.5 per cent myelocytes, 13.5 per cent metamyelocytes, 11.5 per cent staff cells, 36.0 per cent neutrophils and 3.5 per cent normoblasts; the platelet count was 165,000/cu. mm. Repeat liver punch biopsy at this time revealed a diffuse hemosiderosis as before. In addition, there were obvious small foci of cells noted in the sinusoids which were recognized as areas of extramedullary hematopoiesis. These consisted largely of myeloid cells with occasional nucleated red blood cells. On February 3, 1948, a punch biopsy of spleen was obtained. Section of this specimen also revealed several foci of similar hematopoiesis in which eosinophilic granulocytes were plentiful and a few nucleated erythrocytes were recognized.

X-ray studies of the long bones at this time showed no distinct abnormality, although there was some questionable osteoporosis of the right wrist and forearm. A sternal marrow biopsy was therefore performed on February 7 and the histologic sections revealed a hyperplastic cellular marrow containing...
numerous bizarre giant cells and immature granulocytic cells with depressed erythropoiesis (figs. 1 and 2). There was no fibrosis present other than an occasional strand of fibroblasts. A diagnosis of aleukemic myelosis was therefore suggested.

As the patient's prognosis, after another series of blood transfusions, was considered hopeless, he was allowed to go home. He was seen as an outpatient again on May 19, 1948, when his condition was essentially unchanged and he was allowed to remain at home. However, by July 5, 1948, he returned for admission, complaining of generalized weakness, fatigue and upper abdominal distress.

Physical examination now revealed for the first time a soft blowing mitral systolic murmur. There was bilateral venous engorgement of the lower abdominal wall and edema of the lower extremities. The liver and spleen were greatly enlarged, the liver extending to the umbilicus in the midline. There

**Table 2.** Summary of Essential Hematologic Findings

<table>
<thead>
<tr>
<th>Date</th>
<th>Hemoglobin (g/dL)</th>
<th>RBC (10^6/μL)</th>
<th>WBC (10^3/μL)</th>
<th>Myelocyte</th>
<th>Immature</th>
<th>Staff</th>
<th>Neut.</th>
<th>Eosin.</th>
<th>Lymph.</th>
<th>Normoblast</th>
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<tbody>
<tr>
<td>Apr. 11/47</td>
<td>53</td>
<td>3.4</td>
<td>8.0</td>
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<td>—</td>
<td>—</td>
<td>69.0</td>
<td>5.0</td>
<td>26.0</td>
<td>—</td>
</tr>
<tr>
<td>Nov. 28/47</td>
<td>40</td>
<td>1.4</td>
<td>6.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>67.0</td>
<td>6.0</td>
<td>27.0</td>
<td>—</td>
</tr>
<tr>
<td>Jan. 23/48</td>
<td>54</td>
<td>3.3</td>
<td>6.9</td>
<td>1.5</td>
<td>12.5</td>
<td>21.5</td>
<td>36.0</td>
<td>1.0</td>
<td>24.0</td>
<td>3.5</td>
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<td>Mar. 19/48</td>
<td>42</td>
<td>2.6</td>
<td>9.9</td>
<td>2.0</td>
<td>5.0</td>
<td>16.5</td>
<td>41.5</td>
<td>1.0</td>
<td>10.0</td>
<td>4.0</td>
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<tr>
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<td>40</td>
<td>2.2</td>
<td>12.7</td>
<td>3.0</td>
<td>5.0</td>
<td>10.0</td>
<td>42.0</td>
<td>3.0</td>
<td>18.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Sept. 9/48</td>
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<td>8.0</td>
<td>2.0</td>
<td>6.0</td>
<td>34.0</td>
<td>33.0</td>
<td>2.0</td>
<td>12.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Sept. 19/48</td>
<td>66</td>
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<td>—</td>
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were not now, nor had there been before, any palpable lymph nodes. Blood smear showed a leuko-erythroblastic anemia with 9.0 per cent normoblasts, 3.0 per cent myelocytes and 5.0 per cent metamyelo-cytes (see table 2).

With bed rest and multiple transfusions, the edema disappeared, the liver and spleen diminished in size and the hemoglobin rose to 74 per cent. The patient was again allowed to return home on August 16, 1948. However, his condition now assumed a more malignant character so that after an interval of three weeks he was readmitted with severe dyspnea, gross enlargement of liver and spleen and definite cardiac enlargement. The hemoglobin had fallen in three weeks to 16 per cent (table 2). Transfusions were given as before but now produced severe chills on two occasions. When the hemoglobin had risen to 66 per cent a punch biopsy of the sternum was repeated on September 19, 1948. The histologic sections now revealed definite fibrosis of the marrow, largely replacing the hyperplastic tissue though such foci were still present and large giant cells of megakaryocyte type were still prominent (fig. 3). This biopsy was obtained from a fresh site so that the above noted fibrosis was not due to the previous marrow punctures. As before, the patient's condition was again temporarily improved over the next three weeks with multiple transfusions. A bone biopsy from the upper third of the tibia was taken on October 19, 1948. These sections revealed complete replacement of the marrow cavity by dense collagenous fibrous tissue (fig. 4). On November 2, 1948, while sitting in bed talking to his neighbor, he suddenly collapsed and died within a few minutes.

**Postmortem Findings**

**General:** Examination revealed a well nourished, white male measuring 70 inches in length and weighing 160 pounds. Both lungs revealed massive edema and acute congestion. The heart was enlarged, weighing 500 grams; both the right and left ventricles were dilated, the left also being hypertrophied. The myocardium showed the "thrust breast" appearance of fatty change. The septum was the site of an old eroded infarct, being thinned to 2-3 mm. in places. The anterior descending branch of the left coronary
exhibited an old occlusion 3 cm. beyond its orifice. The other branches were patent but sclerosed, calcified and irregularly narrowed.

Gastrointestinal Tract: This was normal throughout. The liver weighed 2700 grams. It felt firm and had a chocolate brown colour. It gave a marked positive prussian blue reaction for hemosiderin. The spleen weighed 1095 grams. It had a deep purple colour and felt rubbery, it was strongly positive for hemosiderin. The cut surface was dry and showed innumerable minute pale gray specks scattered through the pulp. The other viscera including brain showed no noteworthy gross pathology. No enlarged lymph nodes were found. Of the bones, the right femur contained a yellow, gray gelatinous marrow throughout the shaft but at the ends there was red marrow. The sternum, ribs and vertebrae on section revealed a pale gray marrow with no other obvious gross changes. The bones cut readily.

Histologic Examination

Bone: Sections examined from vertebrae, sternum and ribs showed a mixed picture of cellular hyperplasia in some areas with fibrosis predominating in others. In the hypercellular areas the predominating cell had a scanty cytoplasm and a round nucleus of vesicular type with delicate strands of chromatin and in many cases a fairly prominent nucleolus; these were thought to be probably myeloblasts. The remaining cells were obviously granulocytic with eosinophilic myelocytes being prominent. Nucleated erythrocytes appeared diminished though still present. In each low power microscopic field, there were many large giant cells, some of which appeared to be normal megakaryocytes while others had bizarre, hyperchromatic nuclei. (fig. 5). In other blocks from these same bones fibrosis predominated, in some areas this was of delicate nature, strands of plump fibroblasts ranging through the hyperplastic areas (fig. 6), while in others the fibrosis was dense, there being wide bands of collagenous tissue completely replacing the marrow. Some of the bony spicules showed evidence of osteoblastic activity, the majority of them being widened and having a mosaic appearance.

Sections from the mid-femur revealed a fatty marrow with focal areas of cellular hyperplasia. The cellular picture was similar to that described above, many eosinophilic myelocytes being noted together with megakaryocytes. There was no fibrosis or bone sclerosis. These various bone marrow changes were
Fig. 5. Section of vertebral marrow from autopsy showing a hypercellular area of leukemic hyperplasia with numerous bizarre megakaryocytes, similar to first sternal marrow biopsy (compare fig. 1). X 100, H. & E.

Fig. 6. Another section from same vertebra showing fibrous tissue sweeping through the leukemic marrow. Still other blocks showed more marked fibrosis similar to that shown in fig. 4. X 100, H. & E.
interpreted as being of leukemic character with associated fibrosis and bony sclerosis. In the liver the striking feature was the presence of numerous focal collections of marrow cells within dilated sinusoids. These cells were of the same type as seen in the hyperplastic areas of the bone marrow, with many eosinophilic myelocytes and occasional clusters of giant cells with hyperchromatic nuclei, of megakaryocytic type (fig. 7). Nucleated erythrocytes were only occasionally identified. The cords of liver cells were intact but many contained a coarse, light brown granular pigment which proved to be hemosiderin. This was also occasionally seen in swollen Kupffer cells.

An occasional portal tract showed increased fibrous tissue extending into the surrounding liver parenchyma and in these areas there were moderate numbers of round cells present. No areas of hematopoiesis were seen in the portal tracts.

Spleen: The Malpighian bodies were intact and separated by a congested pulp which was diffusely infiltrated with marrow cells similar to those already described. Megakaryocytes were less plentiful than in the liver, though present, and an occasional nucleated red cell was recognized. There were many hemosiderin-containing histiocytes. No positive findings were noted in the other viscera.

**Discussion**

The case presented appears definitely to have been one of atypical granulocytic leukemia (aleukemic myelosis) in which there had been a gradual and increasing fibrosis of the marrow. It thus forms another link in the chain of evidence presented by Heller in his theory that many cases of marrow fibrosis are fundamentally leukemic in character.

It is of great interest that we were able to show extramedullary foci of hematopoiesis in liver and spleen before there was evidence of any extensive marrow...
fibrosis by sternal biopsy. Admittedly, there may well have been fibrosis in other
of the marrow bones, since a biopsy section of one bone must be considered inade-
quate evidence of the state of the entire marrow system. However, this finding
with the fact that at autopsy there was still considerable hyperplastic marrow
remaining, suggests the possibility that the extramedullary hematopoiesis in this
case may have resulted from the same ‘leukemic stimulus’ that involved the
bone marrow and that it did not represent compensatory metaplasia resulting from
loss of marrow by fibrous tissue replacement.

The question as to whether extramedullary hematopoiesis represents leukemic
tissue or is a compensatory mechanism of marrow formation is still controversial.
Heller7 has presented very sound arguments in favor of its being leukemic tissue
formed at the site by the reticulo-endothelial elements of the liver, spleen and
lymph nodes, while he feels that other visceral infiltrates represent colonization
by leukemic cells.

On the other hand, a case of diffuse marrow fibrosis previously studied by one
of us4 showed no histologic evidence of leukemia, the marrow of the sternum,
ribs and vertebrae showing a diffuse fibrosis with osteoblastic changes, and the
femoral marrow being fatty. There was massive extramedullary hematopoiesis
in the liver, spleen, lymph nodes and renal capsules. It is possible that the fibrotic
marrow was the end result of a previous leukemic involvement but there was
nothing to support such a suggestion and this case was classified as idiopathic
marrow fibrosis with compensatory extramedullary hematopoiesis. Similarly in
those cases related to toxins, e.g., benzene, the visceral hematopoiesis cannot be
considered as of leukemic nature.

It thus appears to us that marrow fibrosis should be classified as either primary
idiopathic, for which there is, as yet, no obvious etiology; or secondary to re-
lated causes such as aleukemic myelosis, typical leukemias, neoplasms, toxins,
lipoid metabolic diseases, etc.

The hemosiderosis of liver and spleen in this case is thought to be of physiologic
nature. At the outset, its demonstration in the first liver biopsy proved to be a
false clue, resulting in extensive investigations with the possibility of hemo-
chromatosis in mind. In retrospect, it is felt that this hemosiderosis probably rep-
resented storage of iron released by the breakdown of the red cells, which was
not utilized because of the primary marrow disease with depressed erythropoiesis.
The more marked degree noted at autopsy was undoubtedly related to the multiple
whole blood transfusions which the patient had received. Such an explanation
has recently been offered by Schwartz and Blumenthal17 in cases of exogenous
hemochromatosis following multiple blood transfusions.

Finally, the increased urinary urobinogen in the presence of a normal red cell
fragility to hypotonic saline suggests that the patient’s erythrocytes were ab-
normally sensitive to breakdown by the reticulo-endothelial system. This ab-
normal sensitivity quite possibly was due to the abnormal erythropoiesis in the
marrow and extramedullary foci of hematopoiesis. Hickling14 has previously men-
tioned the increased blood destruction that may be seen in chronic nonleukemic
myelosis and has even suggested that it might be the primary process, the extra-
medullary hematopoiesis being an attempt to compensate for it; we cannot, however, subscribe to this latter theory.

SUMMARY

1. A case of aleukemic myelosis with leuko-erythroblastic anemia is presented, in which the development of extramedullary hematopoiesis in liver and spleen, and fibrosis of marrow was studied by multiple punch biopsies and eventual autopsy.

2. This case offers further support to the theory that many cases of marrow fibrosis are fundamentally leukemic in nature belonging to the group of atypical granulocytic leukemias (aleukemic myelosis).

3. The extramedullary hematopoiesis in this case was interpreted as being of leukemic nature rather than a compensatory metaplasia.

4. Since there are other definite causes of marrow fibrosis and since no adequate etiology has been found to explain some cases, it is suggested that marrow fibrosis be classified as (a) primary idiopathic or (b) marrow fibrosis secondary to aleukemic myelosis, neoplasm, chemical toxins etc.

REFERENCES

1 DONHAUSER, J. L.: Human spleen as an hematoplastic organ, as exemplified in a case of splenomegaly with sclerosis of bone marrow. J. Exper. Med. 10: 559, 1908.
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