Mast Cell Leukemia?—Malignant Mastocytosis with Leukemia-like Manifestations

By P. Efrati, A. KlaJman AND H. Spitz

SEVERAL important works were recently published bearing on the morphology of tissue mast cells (T.M.C.), their development, ontogenetic derivation and distribution in the tissues of various animals and man.1-5. 9 Michels' excellent work covers extensively all the investigations on T.M.C. until 1938. Although research on these baffling cells has continued till the present day, there are differences of opinion concerning their origin and physiologic function. Little is known about their role in human pathology.7, 8, 13, 21

Increase in the number of tissue mast cells is known to occur in a variety of conditions, but of special interest is the marked increase of T.M.C. in the skin, as in the case of urticaria pigmentosa, described many years ago by Unna (Michels8). Lately, new interest in urticaria pigmentosa was aroused by Sagher10 who found associated pathologic changes in the bones. However, Ellis11 already described in 1949, in an infant with congenital urticaria pigmentosa, numerous T.M.C. in lymph nodes, bone marrow, and in other tissues. In 1951, Hissard et al.12 published a case of a new skin disorder (''hematodermie''), which they classified as ''mastocytosis'' and in which they found T.M.C. infiltrations in the skin, in the bone marrow and in the spleen, with invasion of the peripheral blood stream. As far as one could judge from their illustrations the T.M.C. were mainly of the mature type. Degos14, 15 described similar skin lesions with hepatosplenomegaly and enlargement of lymph nodes but T.M.C. were not found in bone marrow and liver. Recently, in an editorial, F. Sagher17 listed a series of pathologic states, ranging from skin diseases to generalized systemic disorders, which were characterized as ''T.M.C. disorders.''' This excellent editorial dealt extensively with the recent advances and newest literature bearing on this subject.

We recently observed a case of what appeared to be leukemia showing numerous T.M.C. in the peripheral blood and bone marrow in various stages of maturation. Since no description of a similar case could be found in the literature, it was decided to report this case fully.

Case Report

A 52 year old widow immigrated to Israel from Poland in 1949. Her past history was noncontributory. The menses had stopped four months before admission. The first symptoms of her illness appeared in 1953, a year before the final admission. She complained, then, of anorexia, upper abdominal pain unrelated to food intake, and vomiting. The pa-
MALIGNANT MASTOCYTOSIS WITH LEUKEMIA-LIKE MANIFESTATIONS

tient lost weight. One month after the onset of her complaints, she was admitted to another hospital where a duodenal ulcer was diagnosed on roentgen examination. At the same time unidentified pathologic cells were noted in the peripheral blood. The spleen was enlarged. The patient was treated with Banthine, her condition improved and she was discharged from the hospital. A month later she was readmitted because of deterioration in her general condition. Marked anemia was found and treated with transfusions. She was discharged four weeks later. On June 13, 1954, she was admitted to another hospital. She was anemic, the spleen and the liver were enlarged. The urine analyses were negative. Blood examination revealed: hemoglobin 8.3 Gm.%, erythrocytes 3.1 millions, hematocrit 29%, leukocytes 8,500. Stabs 3%, segments 28%, eosinophils 18%, lymphocytes 1%.

Of the nucleated elements, 45% were round cells, slightly larger than polymorphonuclears, with a centrally placed nucleus, and basophilic or neutrophilic granules; some of these cells contained a double nucleus. The thrombocytes numbered 70,000. Erythrocyte sedimentation rate was 85 mm/hour (Westergren). Fluoroscopy of heart and lungs did not reveal any abnormalities. Many punched out round areas were noted in the ribs. Roentgenograms of the stomach and the duodenum did not reveal any ulcers. A diagnosis of chronic myelogenous leukemia was made and the patient received urethane, cortisone and three blood transfusions. She felt greatly improved, was discharged from the hospital and was advised to continue the treatment with cortisone which, at home, was gradually decreased to 125 mg. a day.

At first, the patient felt well for seven weeks. Then, a week before admission to our hospital, while being treated with cortisone, she again vomited and complained of tipper abdominal pain which increased on eating. She suffered from severe stomatitis. From time to time red papules and superficial wounds appeared on her body and supposedly disappeared after injections of penicillin.

Physical examination on admission revealed a severely ill, very pale, middle-aged woman. Many small reddish-brown flat papules were noted on chest, abdomen, back, arms and legs. They were covered with small scales. Some of the papules were not pigmented and resembled in color the surrounding skin. The dermatologic picture was not characteristic of urticaria pigmentosa although, on rubbing, few of the papules changed into urticarial wheal. No enlarged lymph nodes were found. No abnormalities of the cardiovascular, respiratory and nervous system were noted. There were few shallow ulcerations on the lips. The tongue was dry and red. On palpation, there was marked tenderness in the right upper abdominal quadrant. The liver was felt 10.5 cm. below the right costal margin and the spleen 9 cm. below the left costal margin. No shifting dullness was noted.

Laboratory data on admission (table 1): hemoglobin 7.9 Gm.%, erythrocytes 2,280,000, leukocytes 3,800: stabs 456 (12%), segments 988 (26%), lymphocytes 76 (2%), eosinophils 950 (25%), unidentified cells 114 (3%). 874 (23%) resembled tissue mast cells of various forms; 798 were disintegrated cells, 3 intermediate in their stage of de
development and 38 mature. The full description of these cells will be given subsequently. Thrombocytes numbered 60,000, hematocrit was 35.5%. Marked anisocytosis and poikilo
cytosis was noted. E.S.R. was 95/128 mm. (Westergren). Clotting time (Lee-White method) 8 minutes, bleeding time 5 minutes, clot retraction was complete in 2 hours. Prothrombin time was 58%, prothrombin consumption 85%. The direct and indirect Coombs' tests were negative. The blood chemistry was within normal limits (see table 3). Urinalyses were negative for albumin, sugar and bile pigment; in the sediment no pathologic elements were found. The electrocardiogram was normal. Fluoroscopy of heart and lungs did not reveal any abnormalities. Examination of the bone marrow on September 10, 1954 (table 2) revealed normal proliferation of the myeloid and erythroid series, marked eosinophilia, erythropagocytosis by macrophages and many T.M.C. Liver biopsy showed a normal liver architecture without infiltration by any abnormal cells. The periportal spaces were normal. Few liver cells showed fatty infiltration.

Subsequent course in the hospital: Sept. 10, 1954-Sept. 17, 1954. The patient had a subfebrile temperature, sometimes reaching 38.2C. Because of the anemia she received two blood transfusions totaling one liter of whole blood.

Sept. 18, 1954-Sept. 22, 1954. The temperature dropped to 37.2 C. After the transfusions,
the hemoglobin increased to 10.7 Gm.%, the erythrocytes to 3 millions, the leukocytes were 6,200 of which 806 were T.M.C. in various stages of maturation (table 1).

Sept. 22, 1954-Sept. 24, 1954. Patient received daily intravenous drip infusions of 20 mg. of ACTH in 800 milliliters of glucose for 3 days. During this time the temperature was normal. However, she complained of severe epigastric pain and the administration of ACTH was stopped. The patient vomited gastric contents without blood for several days afterwards.

On October 3, 1954 we started treatment with folic acid, 300 mg. a day. At the same time the upper abdominal pain decreased greatly and the hyperkeratosis of the skin disappeared. There remained some brownish macules and papules. On rubbing, the urticaria was even more pronounced than before. Biopsy of the skin revealed some mast cells which were, however, not numerous. The histologic picture was not considered to be characteristic of urticaria pigmentosa.

October 16, 1954: patient continued complaining of weakness, anorexia and headache. The temperature reached 38 C. in the evening; patient vomited repeatedly. Many leukocytes were found in catheter urine but no bacilli were isolated from urine cultures. As there was no improvement in the hematologic picture, the administration of folic acid was discontinued. On October 21, the leukocyte count was 5,500 of which 2751 were T.M.C. As the patient's condition deteriorated markedly on October 28, she was again given infusions of ACTH, 20 mg a day. The temperature returned to normal, but because of the recurrence of severe upper abdominal pain, the administration of ACTH was discontinued. Four days later, the leukocyte count reached 17,000 of which 9854 were T.M.C. On November 7, small purpuric spots and blue patches appeared on neck, arms and legs. The patient became apathetic and hoarse. The thrombocyte count fell to 15,000, the bleeding time was 5 minutes, the clotting time 7½ minutes, there was no retraction of the clot after 48 hours. On November 7, the leukocyte count rose to 62,000 of which 50,360 were T.M.C. and 3,125 eosinophils (table 1). The same day, the patient received 300 mg of cortisone intramuscularly; this dose was subsequently reduced to 150 mg a day. In spite of the treatment with cortisone her condition deteriorated rapidly. The ecchimoses reappeared on various parts of the body. There was bleeding from the nose, the hoarseness persisted, the patient vomited repeatedly and refused food. Her face became puffy and the legs edematous. After injection of 2 cc of mersalyl, she passed a liter and a half of urine and the edema decreased. Three days after the commencement of cortisone treatment the leukocyte count decreased.
MALIGNANT MASTOCYTOSIS WITH LEUKEMIA-LIKE MANIFESTATIONS

**Table 2.—Differential Count of Bone Marrow Elements**

(500 cells counted)

<table>
<thead>
<tr>
<th></th>
<th>9/10/54</th>
<th>10/17/54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleated cells, white and red series</td>
<td>70.8%</td>
<td>61.2%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>11.2%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Mast Cells</td>
<td>18.4%</td>
<td>26.2%</td>
</tr>
<tr>
<td>Disintegrated</td>
<td>1.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Young</td>
<td>0.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10.8%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Mature</td>
<td>4.8%</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

**Table 3.—Laboratory Values**

<table>
<thead>
<tr>
<th></th>
<th>9/12/54</th>
<th>9/22/54</th>
<th>11/10/54</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.S.R.</td>
<td>95/128</td>
<td>90/111</td>
<td>40/92</td>
</tr>
<tr>
<td>Urea</td>
<td>34 mg%</td>
<td>31 mg%</td>
<td>28 mg%</td>
</tr>
<tr>
<td>Glucose</td>
<td>108 mg%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total proteins</td>
<td>6.4 Gm%</td>
<td>7.0 Gm%</td>
<td>5.6 Gm%</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.0 Gm%</td>
<td>4.2 Gm%</td>
<td>3.5 Gm%</td>
</tr>
<tr>
<td>Globulin</td>
<td>2.4 Gm%</td>
<td>2.8 Gm%</td>
<td>2.1 Gm%</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.2 mg%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>86 mg%</td>
<td>134 mg%</td>
<td></td>
</tr>
<tr>
<td>Cholesterol ester</td>
<td>52 mg%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>2.7 mEq/l</td>
<td>5.0 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>4.2 mEq/l</td>
<td>5.2 mEq/l</td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>130 mEq/l</td>
<td>130 mEq/l</td>
<td>133 mEq/l</td>
</tr>
<tr>
<td>Cl</td>
<td>87 mEq/l</td>
<td>93.5 mEq/l</td>
<td>90 mEq/l</td>
</tr>
<tr>
<td>K</td>
<td>3.45 mEq/l</td>
<td>5.5 mEq/l</td>
<td>4.2 mEq/l</td>
</tr>
<tr>
<td>Uric acid</td>
<td>2.8 mg%</td>
<td>3.2 mg%</td>
<td>2.3 mg%</td>
</tr>
<tr>
<td>Thymol flocculation</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thymol turbidity</td>
<td>2-3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>58%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Prothrombin consumption</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To 30,000 of which 22,800 were T.M.C. and 300 eosinophils and three days later to 15,700 with 10,550 T.M.C. and 157 eosinophils. Two days later the cortisone was withdrawn because of further rapid deterioration in her general state. On November 17, she vomited blood, passed tarry loose stools, became completely confused and expired the next day.

**Hematologic Observations**

**Peripheral Blood**

As reported in table 1, the hemoglobin levels varied between 8 and 9 Gm. % and, only after repeated transfusions, reached 11.4 Gm. %. Terminally, it dropped to 4.8 Gm. % because of hemorrhages. Concomitant changes were observed in the number of erythrocytes which varied between 2.2 and 3.2 millions. The number of white blood corpuscles increased gradually from 3,800 to the maximum of 62,000 of which T.M.C. constituted from 22 % to 76 %. The number of eosinophils varied from 670/cu. mm to 3100/cu. mm. During cortisone treatment, the number of eosinophils decreased from 3100/cu. mm to 157/cu. mm and two
days before death no eosinophils were found in the peripheral blood. Occasionally few neutrophilic myelocytes and metamyelocytes were seen. A few basophilic granulocytes were observed only twice. Few normoblasts were seen. The number of blood platelets decreased from the first count of 60,000 to 15,000.

**Tissue Mast Cells**

The tissue mast cells were tentatively classified into three groups: mature cells, young cells and intermediate cells—a transitional stage between the young and mature cells. This classification was based mainly on the properties of the cytoplasm and the granules and less on the characteristics of the nucleus. The staining technic used was May-Grünwald and Giemsa and in some cases toluidine blue. The following descriptions were based on observations made on many thousands of cells. There were some characteristics common to all the cells notwithstanding their stage of development. The cells were round or oval in shape, some elongated with tail-like or pseudopodia-like projections. The nucleus was round, oval, indented, kidney-shaped or elongated and twisted occupying from one third to one half of the cell's area. Occasionally, binucleated cells were seen. Usually, the nuclei were of equal size, sometimes one was larger than the other.

**Mature Cells**

The mature cells varied considerably in size. The small round and oval varieties measured from 13.5 x 13.5 micra to 15 x 21 micra, while the elongated ones
measured from 18 x 12 micra to 18 x 42 micra. In the "tailed cells" the diameter of the thick portion was 15 x 15 micra, the tail was up to 27 micra in length and 3 micra to 4.5 micra in width. The cells were tightly packed with granules and thus the protoplasm was rarely seen; it was faintly basophilic and homogeneous. The granules differed in size from fine to coarse measuring up to 3 micra in diameter. They were usually round, rarely rod-shaped, often there was clumping of the granules into a homogeneous mass. The granules varied in color from salmon-red to purple, violet or almost black. Occasionally, the granules consisted of a dark purple peripheral ring, while the center was much lighter in hue. The granules were scattered over the nucleus covering it sometimes completely. The nucleus, which was usually poorly outlined because of the covering granules, was oval or round from 9 x 9 micra to 12 x 7.5 micra in diameter, with loose chromatin structure and without any characteristic pattern. In some cells, perhaps degenerating ones, vacuoles of different sizes were seen, they were unstained or pinkish.

Young Cells

The young cells were generally smaller than the mature ones, less pleomorphic, mostly round or oval, varying in size from 9 x 12 micra to 22.5 x 12 micra, sometimes resembling big lymphocytes or monocytes. The cytoplasm formed a thin rim around the nucleus; sometimes it was more abundant, stained basophilic, rarely the basophilia was marked. The granules were few in number or entirely absent. They were small or dust-like and stained purplish. Clumping of granules was seen in form of a cap lying beside the nucleus. The nuclei were oval or round, indented or kidney-shaped 7.5 x 9 micra in diameter. In few cells a pale nucleolus was noted. Vacuoles of varying size were occasionally noted in the cytoplasm.
Intermediate Cells

As already stated, these cells are intermediate between the young and the mature forms and hence resemble both types. The basophilic protoplasm was clearly seen. The granules were always present, they varied in number and were of different size. Sometimes the granules in the center of the cells were finer and lighter in color than those in the periphery. The nucleus was clearly seen, was round or oval; rarely a nucleolus could be distinguished.

Disintegrated Cells

Numerous disintegrated cells were observed. Around the nucleus many granules of different size were scattered. The cytoplasm could not be distinguished and no cell boundaries could be made out.

Bone Marrow

Two bone marrow examinations were carried out (see table 2). The T.M.C. constituted 18.4% and 26.2% of all the nucleated elements. The respective percentage of the eosinophils was 11.2% and 11.6%. There was no difference between T.M.C. encountered in the peripheral blood and in the bone marrow. The erythropoietic and myeloid elements were normal.

Mitoses

Only once a mitosis of a T.M.C. was seen in the peripheral blood and a few times in the bone marrow.

Toluidine Blue

On staining with toluidine blue the granules of T.M.C. stained metachromatically purplish, the protoplasm was faintly blue and the nucleus pale.
MALIGNANT MASTOCYTOSIS WITH LEUKEMIA-LIKE MANIFESTATIONS

AUTOPSY FINDINGS

The body was that of a poorly nourished elderly female. There was no peripheral edema. The entire skin showed a slight yellowish tinge. The heart weighed 315 grams and showed marked hyper trophy of the left ventricle.

The right lung weighed 615 grams, the left 310 grams. In the right lower lobe and in the base of the right middle lobe, at its mediastinal aspect, there were confluent areas of reddish gray consolidation with multiple yellow foci of necrosis. In the right upper lobe, similar, somewhat brighter foci were noted. The bronchi contained purulent exudate and were lined by congested swollen mucosa.

Spleen was markedly enlarged and weighed 2080 grams. It was widely attached to the diaphragm by extensive fibrous adhesions. The parenchyma was firm, reddish, pouting, fleshy, with paler irregular bands criss-crossing in all directions.

Alimentary Tract. In the lower one half of the esophagus, there were streaky erosions of the mucosa and above the cardia a broad shallow ulcer 2 cm. in diameter was noted. In the duodenum, multiple ulcers were found, one lying just beyond the pylorus on the posterior wall measured 2 to 3 cm. in diameter. Its floor was made up of dense scar tissue which penetrated into the head of the pancreas. Lateral and posterior to that lesion, a small acute ulcer was found, which had penetrated the entire thickness of the wall. The lack of inflammatory reaction around it suggested agonal perforation. A short distance cranial to the papilla of Vater, two irregular shallow ulcers with hemorrhagic base were noted. The larger one measured 2 X 1.5 cm. One similar ulcer was present below the papilla. In that area, the mucosa showed also multiple hemorrhagic erosions.

Liver. Weighed 2920 grams. It was firm and showed a pouting cut surface with a yellowish sheen and accentuated lobular markings.

Endoerines revealed no important lesions. The adrenals were of average size. The cortex was dull tan suggesting a decreased lipid content.

Bone and Bone Marrow. The vertebral bodies were composed of rather densely woven cancellous bone with pale marow. The sternum was essentially similar except for a few areas where the bony meshwork was wider and contained abundant red marrow. Section through the mid portion of the femur revealed bloody fluid but hardly any tissue.

Brain weighed 1120 grams and showed no gross lesions.
New formation of bone in pre-existing wide marrow space (vertebra). H + E, 30X.

Fig. 10. Detail of densely woven, plexiform new bone. H + E, 90X

Microscopic Examination

Spleen. The architecture was much altered. The lymph follicles were almost completely absent and the entire section had a rather uniform appearance. The sinus endothelia and the reticulum cells of the pulp were increased in number and size and there was a considerable cosinophilic infiltrate. Occasional sinusoids contained groups of nucleated red cells and occasional megakaryocytes. Giemsa stains revealed between the reticulum cells a
varying number of mononuclear cells scattered singly or arranged in clusters, containing within the cytoplasm purple granules of various sizes, scattered diffusely or clumped at one side of the nucleus. Sometimes, these granules were so numerous as to obliterate the nucleus. Some cells contained only few granules. The nuclei were vesicular or compact, usually round and occasionally somewhat indented, reniform.

Liver. In the portal areas, there was an infiltrate of large mononuclears with oval to reniform vesicular nuclei and a moderate amount of cytoplasm. Occasionally, eosinophils and few mast cells were demonstrated in these areas. The sinusoids contained an increased number of mononuclears similar to those found in other capillaries. Mast cells were easily demonstrated by Giemsa stains in the portal areas, but none were identified in the sinuses.

Tonsil showed atrophy and fibrosis. In the capsule, many mature mast cells were noted.

Kidneys showed an interstitial infiltrate of mononuclears in the subcapsular cortex and in the peripelvic fat. Occasionally, these cells distended glomerular loops. Fresh and old hemorrhage was present in the mucous membrane of a calix and in the surrounding fat. In both the hilar and the cortical infiltrates many mast cells were demonstrated by Giemsa stains.

Lymph Nodes. Sections from mediastinal and abdominal lymph nodes showed considerable distortion of the architecture by chronic inflammatory changes (infiltration with plasma cells, reticulum cell hyperplasia and sinus catarrh as well as infiltration with eosinophils and occasional megakaryocytes). In and around the capsule, occasional mast cells were noted, but hardly any were demonstrated in the lymph node proper.

Bone. Sections of vertebral body showed wide marrow spaces, packed with hemopoietic cells as well as sheets of mononuclears resembling reticulum cells and, in some areas, fibroblasts. These reticular elements merged with cells that contained similar nuclei and few to many granules that were uneven in size and that took a purple hue with Giemsa stain. The granules were often clumped on one side of the nuclei. In general, these cells were not numerous and were often overshadowed by eosinophils. In addition, foci of newly formed bone were observed in form of a densely woven network of osseous trabeculae lying within the framework of the preexisting bone. In the osteoblastic rims, no mast cells were demonstrated.

In the duodenum there were two acute superficial ulcers with scant inflammatory reaction. Scattered loosely through the submucosa were a moderate number of mast cells.

Sections of pancreas, adrenals and parathyroids added no significant information.

The capsule of the pituitary was widely infiltrated by mononuclear cells, resembling reticulum cells with many eosinophils interspersed. Occasionally, purple granules were demonstrated in some of these cells.

**Discussion**

We feel that the case just described could be classified as tissue mast cell leukemia, although the term leukemia is usually restricted to the pathological changes in the normally found nucleated cells of the blood, bone-marrow and lymphatic tissue. Our case fulfills the criteria generally accepted for other leukemias, i.e., increase in number of nucleated cells in the peripheral blood, appearance of immature forms of the same series, and infiltration of various organs by these cells associated with anemia, thrombocytopenia, hepato-splenomegaly and progression of the disease in spite of treatment. Invasion of the blood stream by tissue mast cells has been previously described by Hissard. The mast cells in the blood stream appeared to be mature. The hematologic manifestations in his case would therefore correspond to "leukocytosis" rather than to leukemia.

The mature cells observed in our case in the peripheral blood stream resembled those occasionally seen in normal human bone marrow, and gave, as mentioned above, a typical staining reaction with toluidine blue. The young cells
were identified by the similarity with mature cells of their nuclei and of the granules, which were tinctorially and morphologically similar to those in the mature cells but differed in number and distribution.

The derivation of these cells suggests itself from the histologic observations. Tissue mast cells were found in close topographic association with reticulum cell proliferations in the spleen. The individual mast cells showed nuclear characteristics of reticulum cells and contained small numbers of typical granules. It also appeared as if one could trace transition from reticulum cells to more and more differentiated forms of tissue mast cells. On the other hand, the number of tissue mast cells was increased in areas that generally abound in connective tissue cells, such as the loose arcular tissue around the tonsils and the peripelvic fibroadipose tissue at the hilum of the kidneys. It would therefore seem that the tissue mast cells are derived both from the reticulum cells and from fibroblasts, or from their precursor, the undifferentiated mesenchymal cell.

In this connection it should be pointed out that tissue mast cells were not numerous in the bone marrow in this case, neither in the aspirate which was examined on two occasions, nor in the sections prepared postmortem. Bone marrow aspirations showed 18.4% tissue mast cells the first time and 26.2% of all cells counted the second time. This would suggest that the mast cell proliferation was not localized primarily in the bone marrow. Of all the blood forming organs, only the spleen showed a considerable number of tissue mast cells that appeared to originate there. In the liver, they were increased in number only in the portal areas but did not seem to proliferate in the sinusoids even though the number of nucleated blood cells was increased in the capillaries. This increase was apparently an expression of the leukemic state.

It should be mentioned that the search for mast cells in the tissues is beset by various technical problems. The cells are fragile and the granules soluble in watery solutions; thus, a number of nucleated cells in the blood stream and in the blood forming tissues may escape identification of their true nature in postmortem material. The young forms are particularly susceptible to damaging influences. Fixation of the tissues also affects the appearance of these cells. After Zenker's fixation, for instance, the granules take on a bright red hue and therefore resemble more closely eosinophilic myelocytes and may be differentiated from them only by careful examination of size, shape and distribution of the granules. This difficulty was present also in our case. In our sections, the mast cells were more easily identified in Giemsa stained material, than by toluidine blue, for reasons unknown to us.

The association of tissue mast cells and eosinophils both in the peripheral blood and in the tissue is quite striking, as shown in table 1. The eosinophils rose at times to 3000 per cubic millimeter in the peripheral blood. In the tissues, marked eosinophilia was present especially in spleen and bone marrow. The frequent association of these two cell types is well known and recently was the subject of special investigations on lesions of the skin. The possible physiologic significance of this association was recently discussed in a stimulating editorial by Riley. Jadassohn commented already in 1939 about the appearance of eosinophils around accumulations of T.M.C. in skin papules following local irritation.
Another interesting feature of our case is the focal osteosclerosis in the vertebrae. Roentgenologic bone changes had been previously reported by Sagher et al. and were noted also in our case in the ribs. Unfortunately the anatomic examination of the skeletal system was not correlated with the X-ray finding and therefore, we are unable to describe the anatomic substrate for the roentgenologic picture. At any rate, the roentgenologists described areas of increased translucency in the rib, whereas our anatomic examination revealed new formation of densely woven plexiform bone in the meshes of the original osseous framework of the vertebrae. Mast cells were not demonstrated near the endosteum as described by Ellis. The stimulus for this proliferation of bone is not clear. Osteosclerosis as a response to metastatic invasion of bone marrow by carcinoma is well known. The pathogenesis of this response is less well understood. Whether or not mast cell infiltration exerted a similar influence in this case, remains a matter for speculation. Post mortem examination, at any rate, failed to demonstrate significant accumulations of mast cells in those areas.

The clinical picture of the disease resembled grossly that of leukemia. The illness was progressive from admission to admission and the high blood count responded at first to treatment with urethane and cortisone. In the earlier phase of observation, we could not exclude the possibility of an aplastic condition in the bone marrow, since there was anemia, thrombocytopenia and leukopenia (3800 white blood cells). We therefore treated the patient with large doses of folic acid. She received 300 mg. daily for a period of 8 days. We observed no improvement in the patient's condition and this treatment was not followed by any immediate significant rise in the number of tissue mast cells in the blood. Such a rise was not observed until 2 weeks after the discontinuation of folic acid therapy.

In our hospital, cortisone administration was followed by a decrease in the number of nucleated cells in the peripheral blood from 60,000 to 15,000. The mast cells were reduced from 50,360 to 10,350 and the eosinophils from 3125 to 157. These changes occurred within six days after initiation of treatment. The influence of cortisone on tissue mast cells had been studied by Bloom who examined multiple mast cell tumors in dogs. Following cortisone administration there was rapid regression in the size of the tumors and histologically, the tissue mast cells showed degeneration, destruction and disappearance. Unfortunately, in our case, we were not able to observe the more prolonged influence of therapy since 8 days after onset of treatment, the patient's general condition deteriorated rapidly and she succumbed to massive intestinal hemorrhage originating in multiple fresh erosions in the duodenum, probably as a result of cortisone administration.

A tentative classification of mast cell disorders was recently given by Sagher. Our case does not correspond fully to any of the so far published groups of this disorder but represents a type of its own.

**Summary**

A case of probable leukemia in an adult female is described which is classified as tissue mast cell leukemia. Clinical course and autopsy findings are analyzed...
and a detailed morphologic description is given of the different stages of matura-
tion of T.M.C. as found in the peripheral blood and in bone marrow aspirates.

The patient succumbed to massive gastrointestinal hemorrhage following corti-
sone treatment.

Histologic examination of spleen and loose areolar tissue suggested origin of
T.M.C. from both reticulum cells and fibroblasts.

Focal osteosclerosis in the vertebrae probably represents a lesion related to
the basic disorder.

SUMMARIO IN INTERLINGUA

Es describite un caso de leucemia probabilmente occurrente in un feminina
adulte. Illo es classificate como leucemia mastocytic tessutal. Le curso clinico e le constata-
tiones necropsiche es analysate, e un detaliate description morphologic es date de
omne le varie stadios de maturation del mastocytos tessutal que esseva trovate
in le sanguine peripheric e in aspiratos de medulla ossee.

Le patiente succumbeva a massive hemorrhagias gastrointestinal post tracta-
mento con cortisona.

Le examine histologic del splen e de areas usualmente containente un abund-
antia de cellulas de tessuto conjuntive supportava le conclusione que le masto-
cytos tessutal habeva lor origine in cellulas reticular e etiam in fibroblastos.

Osteosclerosis in le vertebrae representava probabilmente un lesion relationate
al disordine fundamental.

REFERENCES

Thieme Verlag, 1950.
et réactions de l'organisme déclenchées par l'implantation sous cutanée d'un caillot
sanguin. La Revue de Pathologie Générale et Comparée No. 646, p. 401–423, 1953
(March).
Experimentalnoy Biologii i Medicini 40: 70, 1955.
9. Compton, Ariel S.: A cytochemical and etiological study of the connexitve tissue mast
10. Saghier, F., Cohen, Ch. and Schor, S.: Concomitant bone changes in urticaria pig-
426, 1949.
de Médecine 52: 584, 1951.
13. Debios, R.: Urticaria Pigmentaria J otros tipos de Mastocytosis. Actas Dermo-Sifilo-
Nos. 5 & 6, p. 111, 1956.
MALIGNANT MASTOCYTOSIS WITH LEUKEMIA-LIKE MANIFESTATIONS


22 Jadassohn. Cited by Bremy.3
Mast Cell Leukemia?—Malignant Mastocytosis with Leukemia-like Manifestations

P. EFRATI, A. KLAJMAN and H. SPITZ