Chediak’s Anomaly of Leukocytes in Malignant Lymphoma Associated with Leukemic Manifestations: Case Report with Necropsy

By P. Efrati and W. Jonas

Chediak, in 1952, published the first case of an anomaly of leukocytes, which was named after him. The patient was a young boy who died two years after the examination. In addition to the leukocyte anomaly he exhibited hepatosplenomegaly, lymphadenopathy, anemia, thrombocytopenia and neutropenia. The boy and his three brothers were albinos with marked photophobia. They all died before the age of seven years from repeated infections. Unfortunately no necropsy was performed. The parents were cousins.

In 1954, Higashi published the second case of Chediak’s anomaly in an 11-month-old Japanese boy whose parents were cousins; his three brothers had died previously. In addition to the signs observed by Chediak there were changes in the skin compatible with xeroderma pigmentosum.

In 1957, Donohue and Bain from Toronto, described the third case. Their patient, a girl, aged two years and ten months, suffered from marked photophobia, thirst, profuse perspiration, repeated infections and skin rashes. Her hair was fair, very dry and sparse. She presented various neurologic symptoms, generalized lymphadenopathy and hepatosplenomegaly. She died 18 months after the first examination and in the last weeks was jaundiced. The necropsy revealed diffuse infiltration of all the organs with peculiar round cells, severe inflammatory changes in the lungs and the nervous system. The parents were not related.

In 1955, we observed a case of Chediak’s anomaly with leukemic manifestations. The child died soon afterwards and necropsy revealed changes characteristic of a malignant lymphoma. We believe that our case may add additional light to the understanding of this anomaly.

Presentation of Case

A. M., an 11-month-old boy, was admitted to the hospital on June 2, 1955, because of a febrile disease of 5 days duration. His parents had immigrated to Israel from Iraq. He was the first born; their other child, a baby girl, was healthy. The parents were not related. In February, 1955, he was hospitalized because of bronchopneumonia which complicated measles. At that time stool cultures revealed Shigella Flexner; hemoglobin 7.8 Gm. per cent, erythrocytes 3,280,000, leukocytes 6,350. No abnormality of leukocytes was noted.

A few days before the present admission the mother noticed enlargement of cervical lymph nodes. At home, he was febrile for five days and was treated with penicillin and sulfa without any improvement.

On admission the child was severely ill, the temperature was 40°C. Bilateral purulent otitis was diagnosed; the pharynx was inflamed. Below the left mandibular angle a large lymph node was found; a smaller one was noted on the right side. The lymph nodes were mobile and no signs of inflammation were noted. Wet rales were heard over both lungs.

From the Laboratory for Blood Morphology and the Pediatric Department, Kaplan Hospital, Rehovoth, Israel.

Submitted Dec. 3, 1957; accepted for publication May 15, 1958.
Over the precordium, a grade 2 systolic murmur was heard. Slight pitting edema was noted over the legs. The spleen depassed the costal margin by 8 fingerbreadths and the liver by 4 (see fig. 1.).

**Laboratory investigations:** Hemoglobin 6.3 Gm. per cent; erythrocytes 2.6 millions; leucocytes 75,000; platelets 39,000; reticulocytes 9°/00 (see table 1). Bleeding time was 7 min.; coagulation time (White-Lee) 4 min.; sedimentation rate (Westergren) 60/90. Total bilirubin in serum 0.4 mg. per cent. Blood proteins 6.8 Gm. per cent, albumine 3.3 Gm. per cent, globuline 3.5 Gm. per cent; urea 30 mg. per cent; cholesterol 51 mg. per cent; Weltmann 7–8; alkaline phosphatase 4.2 Bodansky units; thymol flocculation +3; thymol turbidity 10, Paul-Bunnell test ± 1/32. Urinanalysis: traces of albumen and few granular casts.

The roentgen examination of the chest revealed: left lung, a homogenous shadow over the base, increased hilar marking with undulate border; right lung, a homogenous shadow in the cardio-diaphragmatic angle and near the right hilus. These findings were suggestive of enlargement of hilar lymph nodes and infiltration in the lung parenchyma (see fig. 2). X-ray pictures of the skull and the long bones did not reveal any abnormalities.

He was treated with daily injections of penicillin—600,000 units and 40 mg. of ACTH; blood transfusion of 150 ml. of whole blood, and infusions of saline and glucose. His condition remained very critical and five days after admission he died with signs of anoxia.

**Necropsy Finding** (Dr. H. Spitz)

**External Description**

The body was that of a well-developed, pale male child of apparent age of 17 months. There were some injection points over the thighs. No ulceration of the gums was seen.

**Internal Description**

An incision was made from the thyroid notch to the symphysis pubis, revealing some subcutaneous tissue and well-developed pectoral muscles. The cervical glands were numerous, enlarged, soft and fleshy. Pleural, pericardial and intestinal serosal surfaces were smooth and glistening. The peritoneal cavity contained a little excess of straw-colored fluid. The other cavities contained the usual amount of fluid.

**Circulatory System:** The heart was flabby and a little dilated and pale, otherwise it showed no significant change.

**Respiratory System:** The trachea and extra-pulmonary bronchi contained a little mucus.

The left lower lobe was solid and had a light yellow color. The remaining portion was pinkish in color. The right lung had several light yellowish areas, not as extensive as the left.

** Mediastinal Lymph Nodes** were greatly enlarged. A large group of glands was present over the bifurcation of the bronchus, posteriorly.

**Liver** was large and weighed 670 grams. It was greasy and fatty and had a fleshy appearance.

**Gallbladder, Biliary System and Pancreas** showed no significant lesions.

**Spleen** weighed 2,070 grams. It was soft and cellular, with a bright pinkish color.

**Genito-Urinary Tract:** The kidneys were equal in size, the capsule stripped easily, the cortex was smooth, with some light yellowish areas present. The cut surface showed a normal architecture. Ureters and bladder showed no significant lesions.
Gastrointestinal Tract: The esophagus and stomach showed no significant lesions. The mesentery contained masses of glands, enlarged and soft. The intestines and rectum showed no significant lesions.

Thyroid, Adrenals and Testis showed no significant lesions.

Thymus: Numerous glands were adherent to the thymus which was pale, but normal in size.

Brain showed no significant lesions.

Skeletal System: The sternal, vertebral and femoral marrow was reddish in color.

Microscopic Description

Lymph Node: The architecture was completely destroyed (fig. 12). It was replaced by sheets of hyperchromatic cells with a small amount of basophilic cytoplasm and round or oval nuclei with fairly prominent nucleoli. The cells were larger than mature lymphocytes and the uniformity of cell type was striking. Interspersed among these cells were larger cells with vesicular nuclei and a pale, slightly eosinophilic cytoplasm. Many of these cells showed a vacuolated cytoplasm.

Marrow: Replacement of normal marrow by lymphosarcoma cells.

Kidney showed a focal infiltration with cells.

Spleen was very congested, lymphoid follicles had disappeared, heavily infiltrated with tumor cells.

Liver showed a very severe degree of fatty degeneration. Practically all the cells contained fat droplets. The portal areas were heavily infiltrated with tumor cells.

Adrenals: No significant lesions seen.

Lungs showed severe edema. The alveoli were filled with tumor cells and some heart failure cells.

Cytologic Examination of the Spleen (Dr. P. Efrati)

The material was obtained after death. The predominant cells were mature and young lymphocytes, in many of them a round inclusion body was seen in the cytoplasm, sometimes upon the nucleus. Some of the lymphocytes were in mitosis. We also observed phagocytic reticulum cells and large cells with round reticular nucleus, blue round nucleolus and basophilic cytoplasm, but without inclusion bodies. The nuclei of the granulocytes were pale; in the cytoplasm Doehle bodies were noted (fig. 10). The cytologic examination of a lymph node revealed identical changes.

Hematologic Investigation

The Peripheral Blood. Severe anemia and thrombocytopenia were found. The number of leukocytes varied from 55,000 to 82,000. The number of granulocytes did not fall below 4,400 per mm.³, although the mononuclear cells constituted between 87.4 to 91.2 per cent. The neutrophiles were similar to those described by Chediak, Donohue and Bain. In the more mature neutrophiles, polynuclear and staff cells, we observed, in agreement with the other authors, three to six large, irregular, slate-green masses similar to Doehle
bodies (fig. 4). Often these bodies were smaller and more numerous, up to 15 in one cell. In the first examination, 440 of 4,840 neutrophiles in one mm.$^3$ were without Doehle bodies; in the subsequent examinations, they were found in almost all the mature neutrophiles. Few metamyelocytes were observed; their cytoplasmic granules stained gray and were unusually coarse (fig. 5).

The mononuclear cells showed a marked pleomorphism. The most numerous were mature lymphocytes (37.4%, 41.6%, 32.6% of all the nucleated cells.* Of these 41.2%, 28.8% and 56.3% *) contained round inclusion bodies, 2 to 3 microns in size, similar in color to chromatin (fig. 3). Most commonly there was one inclusion body in a cell; in some there were two or three. A different type were the mononuclear cells classified in the table (table 1) as large lymphocytes and cells closely resembling Rieder's cells. In 54 to 97.7* per

*in subsequent counts.
## Table 1.—Differential Count of Leukocytes in Peripheral Blood (500 cells counted)

<table>
<thead>
<tr>
<th>Date</th>
<th>2/6/55</th>
<th>3/6/55</th>
<th>5/6/55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells per 1 cu. mm.</td>
<td>50,000</td>
<td>75,000</td>
<td>82,000</td>
</tr>
<tr>
<td>%</td>
<td>number</td>
<td>%</td>
<td>number</td>
</tr>
</tbody>
</table>

### Neutrophilic cells:
- **Segmented, normal**: 0.6 330 — — —
- **Segmented with Doehle bodies**: 7.4 4,070 8.6 6,450 11.6 9,812
- **Staff cells, normal**: 0.2 110 0.6 450 — —
- **Staff cells with Doehle bodies**: 0.6 350 1.6 1,210 0.6 492
- **Metamyelocytes**: — — 0.2 150 0.4 40

### Mononuclear cells:
- **Lymphocytes**: 20 11,000 23.2 17,400 18.6 15,252
- **Lymphocytes with inclusions**: 14 7,700 9.4 7,050 24.0 19,680
- **Lymphocytes, large and Rieder cells**: 14 7,700 6.4 4,800 1.4 1,148
- **Lymphocytes with inclusions**: 17.4 9,570 16.4 12,900 25.2 20,644
- **Atypical and neoplastic cells**: 2.8 1,540 2.6 1,050 0.6 492
- **Atypical cells with inclusions**: 5 2,760 4.6 3,450 1.6 1,312
- **Plasma cells**: 10.2 5,610 1.4 1,050 11.0 9,020
- **Plasma cells with inclusions**: 0.4 220 23.2 17,400 — —
- **Vacuolated mononuclear cells**: 1.4 770 0.8 690 1.8 1,476
- **Phagocytic mononuclear cells**: 0.2 110 — — —
- **Phagocytic mononuclear cells with erythrophagocytosis**: 1 550 — — —
- **Mononuclear cells in mitosis**: 0.2 110 — — —
- **Mononuclear cells in mitosis with inclusions**: 0.6 330 — — —
- **Mononuclear cells with indented nuclei**: 1.6 860 — — 1.8 1,476
- **Blasts**: 0.6 330 0.2 150 0.2 164
- **Blasts with inclusions**: 0.8 440 — — 1.2 994
- **Unidentified cells**: 1 550 0.4 300 — —
- **Normoblasts**: — — 0.4 300 — —

---

**Fig. 2.—X-ray picture of lung.**
cent of these cells we found inclusion bodies similar to those seen in lymphocytes (table 1). The cells that we considered peculiar to our case were large mononuclears, probably of neoplastic origin. They resembled the atypical monocytes of infections mononucleosis; their nucleoli were indented, with coarse chromatin structure and two to three nucleoli; the basophilic cytoplasm was paler around the nucleus, few vacuoles were seen in the cytoplasm (fig. 7). The characteristic inclusion bodies were also found in the cytoplasm of these cells; sometimes they were superimposed on the nucleus. These peculiar cells varied in size, on the average being between 12 to 24 microns in diameter; sometime it was difficult to distinguish them from Rieder’s cells.

Cells with markedly indented nuclei were counted separately; some of them were probably normal monocytes, while others, with coarse chromatin structure of the nucleus, resembled the atypical cells of infectious mononucleosis. We also counted separately cells with large numbers of small and medium size vacuoli. A large number of plasma cells (table 1), with or without inclusion bodies, was found. In the blood smears taken during the first
few days, cells in mitosis were seen with inclusion bodies. Few of the mononuclear cells showed erythrophagocytosis (fig. 9). Under blast cells we classified cells which were difficult to identify and which exhibited signs of immaturity such as loose chromatin structure of the nucleus, one or more nucleoli and strongly basophilic cytoplasm. In some of these cells were inclusion bodies. It was not always possible to distinguish them from the large neoplastic cells. Interestingly enough, the number of cells with inclusion bodies increased as the disease progressed.

**Bone Marrow** (table 2). The ratio between the cells of the myeloid and the erythropoietic series was normal, 5.2:1. The cells of the erythropoietic series did not show any abnormalities. Marked pathology and pleomorphism
were exhibited by the white cells. A few of the myeloblasts contained coarse azurophilic granules. More pronounced changes were observed in the pro-myelocytes; their azurophilic granules were usually coarser than normal and often were formed into clumps or inclusion bodies. These clumps were frequently found inside large vacuoles, more rarely, the vacuoles contained azurophilic dustlike particles (fig. 6). The granules of the neutrophilic myelocytes and metamyelocytes were grayish, coarse and of different size. The chromatin structure of the nuclei was abnormally coarse. The mature neutrophiles—staff and segments—were similar to those observed in the peripheral blood. The eosinophilic myelocytes and segments were found in normal numbers in the bone marrow, although no eosinophiles were observed in the peripheral blood. The eosinophilic granules were giant, of different size, sometimes few of them completely filling the cells. Clumping of granules was encountered.

All the mononuclear cells, with and without inclusion bodies, described in the peripheral blood were seen in the bone marrow.
CHEDIAK'S ANOMALY OF LEUKOCYTES IN MALIGNANT LYMPHOMA

Fig. 12.—Histologic picture of lymph node.

<table>
<thead>
<tr>
<th>Erythropoietic Series</th>
<th>Mononuclear Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pronormoblasts</td>
<td>Lymphocytes, without inclusions</td>
</tr>
<tr>
<td>Basophile Normoblasts</td>
<td>Lymphocytes with inclusions</td>
</tr>
<tr>
<td>Polychromatophic Normoblasts</td>
<td>Large Lymphocytes and Rieder’s Cells without inclusions</td>
</tr>
<tr>
<td>Orthochromatic Normoblasts</td>
<td>Large Lymphocytes and Rieder’s Cells with inclusions</td>
</tr>
<tr>
<td>Normoblasts in Mitosis</td>
<td>Atypical and Neoplastic Cells without inclusions</td>
</tr>
<tr>
<td>Myeloid Series</td>
<td>Atypical and Neoplastic Cells with inclusions</td>
</tr>
<tr>
<td>Myeloblasts without inclusions</td>
<td>Phagocytes, Erythrophagocytosis</td>
</tr>
<tr>
<td>Myeloblasts with inclusions</td>
<td>Plasma Cells without inclusions</td>
</tr>
<tr>
<td>Promyelocytes, vacuolated</td>
<td>Plasma Cells with inclusions</td>
</tr>
<tr>
<td>Promyelocytes without inclusions</td>
<td>Various Cells</td>
</tr>
<tr>
<td>Myelocytes, eosinophilic</td>
<td>Reticulum Cells</td>
</tr>
<tr>
<td>Myelocytes neutrophilic without inclusions</td>
<td>Cells in Mitosis</td>
</tr>
<tr>
<td>Myelocytes with coarse granules</td>
<td>Unidentified Cells</td>
</tr>
<tr>
<td>Metamyelocytes, neutrophilic with coarse granules</td>
<td></td>
</tr>
<tr>
<td>Staff Cells, neutrophilic without Dohle bodies</td>
<td></td>
</tr>
<tr>
<td>Staff Cells, neutrophilic with Dohle bodies</td>
<td></td>
</tr>
<tr>
<td>Giant Staff Cells</td>
<td></td>
</tr>
<tr>
<td>Segmented, neutrophiles, with Dohle bodies</td>
<td></td>
</tr>
<tr>
<td>Eosinophiles, segmented</td>
<td></td>
</tr>
</tbody>
</table>

The Examination of the Patient’s Family: The blood picture of the mother was normal. In the father the nuclei of the mature neutrophiles showed a coarse chromatin network; the granules were grayish and coarser than normal. We were under the impression that the eosinophilic granules were somewhat coarser than normal. In some of the lymphocytes we found large granules, which, however, did not reach the size of the inclusion bodies seen in our patient.

The boy’s little sister was examined and no abnormal cells were seen in
the peripheral blood and in the bone marrow. The chromatin structure of the neutrophilic polynuclears was somewhat coarser than normal.

DISCUSSION

The case presented here is the fourth of Chediak's anomaly reported in the literature. Contrary to the other publications our case also presented a clinical picture of leukemia, manifested by greatly increased number of leukocytes with immature and pathologic cells in the peripheral blood, anemia, thrombocytopenia, hepatosplenomegaly and lymphadenopathy. The child was not an albino, and no pathologic changes were noted in the skin. The parents were not related.

All of the four cases had in common hepatosplenomegaly, lymphadenopathy and characteristic changes in the leukocytes—Doeble bodies in the neutrophiles and the inclusion bodies in the mononuclears. We also observed the giant eosinophilic granules in mature eosinophiles, which were described by Chediak.

The cells peculiar to our case were large mononuclear cells, often very young; some of them contained inclusion bodies. The necropsy revealed a malignant lymphoma of the lymph nodes with diffuse infiltration of all the internal organs. We believe that these cells were the malignant lymphoma cells which found their way to the blood stream.

Of the other three cases only the one reported by Donohue and Bain came to necropsy. Interestingly enough, in their case, although the changes in the lymphatic system were not compatible with lymphoma, they noted a cellular infiltration of visceral organs with round cells with almost naked nuclei and with dense chromatin pattern. These were presumably lymphocytes. It is difficult to decide whether Donohue's and Bain's case and ours present two different pathologic processes or different stages of the same neoplastic condition of the reticulo-histiocytic system.

We did not perform detailed cytochemical studies of the inclusion bodies, but our staining method of May-Grunwald-Giemsa permits us to draw some conclusions. The Doeble bodies stained bluish-gray, probably due to increased content of ribose-nucleic-acid. The eosinophiles did not present any staining abnormalities and we presume that their granules did not undergo any chemical changes. The inclusion bodies in the mononuclear cells stained purplish like chromatin. This was especially evident in cells undergoing mitosis. Therefore, we believe, that they contain deoxyribose nucleic acid. The azurophilic granules of promyelocytes were often clumped together but retained their azurophilic hue.

It is difficult to decide whether Chediak's anomaly is a hereditary entity; the consanguinity of the parents in two out of four cases, and abnormality in the leukocytes of the other members of the family, seem to strengthen this hypothesis. The other possibility is that we are dealing with a degenerative phenomenon in the leukocytes due to a systemic disease.

It is highly probable that many cases passed undiagnosed. Therefore, a
closer attention should be given to this anomaly to permit a better study and eventual elucidation of its pathogenesis and treatment.

SUMMARY

A case of Chediak’s anomaly of leukocytes was described, the fourth reported in the literature.

The patient was an 11-month-old boy who, in addition to Chediak’s anomaly of the leukocytes, presented a leukemic blood picture.

He died five days after admission to the hospital, and necropsy revealed a malignant lymphoma.

We consider it possible that in all the reported cases there were generalized pathologic changes in the reticuloendothelial system.

SUMMARIO IN INTERLINGUA

Es describite un caso de anomalia de Chediak in leucocytos. Le caso es le quarte in le litteratura.

Le patiente esseva un puero de 11 menses de etate. A parte le anomalia de Chediak del leucocytos, ille presentava un leucemic tableau sanguine.

Le patiente moriva cinquc dies post su admission al hospital. Le necropsia revelava le presentia de un lymphoma maligne.

Nos considera como possibile que il habeva, in omne le reportate casos, generalisate alterationes pathologic in le systema reticuloendothelial.

REFERENCES

Chediak's Anomaly of Leukocytes in Malignant Lymphoma Associated with Leukemic Manifestations: Case Report with Necropsy

P. EFRATI and W. JONAS