MONOCYTIC LEUKEMIA AND TUBERCULOSIS

By Elwyn L. Heller, M.D., and Charles H. Hiles, M.D.

Since the recognition of a monocytic type of leukemia following the report of Reschad and Schilling-Torgau in 1913, enough cases have been observed to warrant its acceptance as an entity distinct from the myeloid and lymphatic varieties.

The present case is of particular interest because it was associated with an active tuberculous infection; the possibility that the hematologic findings may have represented a leukemoid reaction secondary to a widespread tuberculous infection became a major consideration.

REPORT OF A CASE

H. L., a 70 year old retired clergyman, was admitted to the Eye and Ear Hospital of Pittsburgh on September 28, 1945, complaining of severe sore throat, persistent nasal obstruction, frontal headaches, and a low-grade fever of 10 days' duration. "Sinus trouble" had been present for several years. Past history included an appendectomy and incision and drainage of a tuberculous abscess in the lumbar region in 1939, which drained for many months thereafter. A guinea-pig inoculated with the exudate developed generalized tuberculous infection.

Physical examination revealed no sinus tenderness, a swollen, boggy, and crusted nasal mucous membrane, acutely inflamed tonsils, and a granular injected pharynx. Except for pallor and slight pyorrhea alveolaris the gums appeared normal. The blood pressure was 110/65. The physical findings were otherwise normal.

The urine was essentially normal. The erythrocytes were 3,030,000 per cu. mm.; the hemoglobin was 75 per cent; the white blood cell count was 11,950 per cu. mm. Abnormal cells were noted in the blood smear, which was subsequently examined and diagnosed as monocytic leukemia by Dr. Mortimer Cohen.*

A dental consultant advised extraction of the teeth, but the procedure was considered inadvisable because of the patient's weakened condition and the hematologic findings. Therapy with penicillin, begun on admission and continued for 9 days, was discontinued after a total dose of 1,040,000 units. The patient was transferred to the service of Dr. R. R. Snowden at the Presbyterian Hospital on October 16, 1945. He complained chiefly of weakness, and his condition rapidly deteriorated. Lethargy, pallor, and mental depression were extreme. Pleural effusion, pleural and pericardial friction sounds were noted several days before death, which occurred on November 14, 1945, less than 7 weeks from the admission to the hospital.

Roentgenologic examination of the chest on October 20 revealed enlargement of the left ventricle, bilateral pleural effusion, and calcified nodes at the lung roots. The laboratory findings were essentially normal, excepting those of the blood. The results of several blood counts are recorded in table 1.

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* Died June 20, 1946.
MONOCYTIC LEUKEMIA AND TUBERCULOSIS

POSTMORTEM FINDINGS

The autopsy was performed 2 hours after death. The body appeared wasted, the skin was sallow, and numerous petechial hemorrhages were noted over both flanks. The axillary and inguinal lymph nodes were discrete, moderately enlarged, and rounded. The edge of the liver was palpable 9 cm. below the lower costal border. An incisional scar in the right lumbar region was well healed. There were no other noteworthy abnormalities on external examination.

The pleural cavities each contained approximately 700 cc. of clear watery fluid. The pleural surfaces were irregularly thickened, scarred, edematous, and studded with pale miliary nodules. There were numerous fibrinous and fibrous adhesions between the parietal and visceral pleura.

The lungs were voluminous and poorly aerated. On section moderately extensive congestion and edema were noted, most pronounced in the dependent portions. The pericardium was thickened, fibrous, and its cavity was almost totally obliterated by adhesions. The spleen weighed 405 grams and was uniformly bluish-purple. On section the parenchyma was uniformly soft and reddish-brown. The liver weighed 1890 grams. It presented no gross abnormalities. On section of the right kidney thick purulent exudate escaped from the cavity of the pelvis. A papillary tumor involved approximately half of the inferior pelvic surface; it did not appear to extend into the overlying renal medulla. The ureteral orifice at the ureteropelvic junction was occluded by the tumor.

The axillary, inguinal, peribronchial, mediastinal, mesenteric, and paravertebral lymph nodes were moderately enlarged. Nodes of the latter group measured up to 4 cm. in diameter. They were discrete, their capsules were thin, tense, and intact. On section the pulp was solid, pale, and fleshy. No areas of degeneration or necrosis were apparent.

The marrow of the vertebral bodies and ribs was uniformly deep red and hyperplastic in appearance. The bony trabeculae of the spongiosa were softened and cut readily.

There were no additional gross abnormalities of significance.

MICROSCOPIC EXAMINATION

Lungs: The pleura was thickened by fibrous tissue containing typical nodular tubercles frequently well organized by scar tissue. In areas there was a heavy diffuse infiltration with large cells of monocyte type, many of which appeared immature. The cytoplasm was abundant, pink, nongranular, and frequently irregular in contour; the nuclei were large, vesicular, and frequently lobate. In the pulmonary parenchyma there were numerous perivascular infiltrations with monocytes which frequently had caused considerable thickening of the alveolar walls. Immature forms were numerous. Serous fluid distended many of the alveolar spaces, which contained mature monocytes in small numbers. Purulent

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**Table 1**

<table>
<thead>
<tr>
<th>Date, 1945</th>
<th>R.B.C.</th>
<th>Hb.</th>
<th>W.B.C.</th>
<th>P.M.N. Myelocytes</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Pro-monocytes</th>
<th>Blasts</th>
<th>Additional</th>
</tr>
</thead>
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<tr>
<td>Oct. 19 ...</td>
<td>2.90</td>
<td>60</td>
<td>32,500</td>
<td>2.1 7 64 8 0</td>
<td>Occasional nucleated R.B.C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oct. 23 ...</td>
<td>2.50</td>
<td>56</td>
<td>43,000</td>
<td>1.1 4 6 60 5 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oct. 29 ...</td>
<td>2.41</td>
<td>56</td>
<td>50,300</td>
<td>1.7 3 2 76 2 0</td>
<td>4 nucleated R.B.C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov. 1 ...</td>
<td>4.00</td>
<td>28</td>
<td>44,000</td>
<td>3 8 46 18 0</td>
<td>11 nucleated R.B.C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov. 3 ...</td>
<td>2.15</td>
<td>54</td>
<td>58,500</td>
<td>2.1 3 74 1 3</td>
<td>9 nucleated R.B.C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nov. 6 ...</td>
<td>2.15</td>
<td>54</td>
<td>55,900</td>
<td>1.6 1 4 78 1 0</td>
<td>2 nucleated R.B.C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nov. 8 ...</td>
<td>2.15</td>
<td>54</td>
<td>72,000</td>
<td>1.9 1 5 68 8 1</td>
<td>7 nucleated R.B.C.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nov. 13 ...</td>
<td>2.15</td>
<td>54</td>
<td>100,500</td>
<td>2.3 2 6 44 16 9</td>
<td>14 nucleated R.B.C.</td>
<td></td>
<td></td>
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</table>
Fig. 1. Blood Smear Showing Two Monocytes and a Neutrophil. X 1250

Fig. 2. Liver Showing Diffuse Cellular Infiltration and Compression of the Hepatic Cords. X 300
FIG. 3. **Lymph Node. Miliary Tubercles Are Surrounded by Inflammatory and Fibroblastic Tissue.**

$\times 120$

FIG. 4. **Bone Marrow. The Cellular Proliferation Has Replaced the Fat and Hematopoietic Tissue.**

Note compression atrophy of the bone lamella. $\times 120$
FIG. 5. Testis Showing Diffuse Interstitial Infiltration. × 130

FIG. 6. Testis. The Monocytic Characteristics of the Cells Are Evident. × 800
MONOCYTIC LEUKEMIA AND TUBERCULOSIS

392

exudate was present in the lumen of a few bronchioles, surrounding which were small pneumatic foci. No tuberculous involvement of pulmonary parenchyma was demonstrable.

Heart: The epicardium was considerably thickened by vascular scar tissue within which were nodular, well-organized tubercles. Throughout the myocardium were numerous small irregular interstitial infiltrations with cells of the monocytic series, which were present in considerable numbers in the vascular lumina. The tuberculous reaction had not extended beneath the epicardium.

Spleen: The pulp was unusually cellular but the essential structure of the organ was not significantly altered. The lymphoid follicles were distinct and frequently atrophic. Throughout the interstices of the pulp were mononuclear cells of monocyte type, so numerous as to cause compression and distortion of the sinusoidal spaces. They intermingled with smaller numbers of lymphoid cells and scattered plasma cells and neutrophilic leukocytes. Within the sinuses in small numbers were monocytic cells which were morphologically indistinguishable from the reticulo-endothelium. No tuberculous involvement was apparent.

Liver: In some of the portal areas there were small infiltrations with monocytic cells. Identical cells were present in profusion throughout the sinuses, in some regions causing compression and atrophy of the hepatic cords. The Kupffer cells generally were hypertrophied and could be distinguished from the monocytic cells merely by their position along the sinusoidal walls. There was no suggestion of a tuberculous reaction.

Kidneys: Interstitial infiltrations of the parenchyma with mononuclear cells were numerous. They were generally perivascular. The pelvic epithelium of the right kidney had been converted into an extensive neoplasm composed of closely approximated papillary projections covered with epithelium of transitional cell type showing stratification, loss of polarity, and scattered mitotic figures. There was no sign of invasion of the renal parenchyma. There was no evidence of tuberculosis in either kidney.

Lymph Nodes: Sections of the nodes from various regions revealed an extensive inflammatory reaction exhibiting typical miliary and small conglomerate tubercles, and small foci of caseous necrosis throughout a fibroblastic matrix.* In some nodes, uninvolved by the tuberculous process, there was a diffuse infiltration of the pulp tissue with cells of the monocytic series, which frequently extended into and through the capsule into the perinodal fat. The reticulo-endothelial cells were hypertrophied, frequently epithelioid, and appeared free in the sinusoidal lumina in moderate numbers.

Bone Marrow: Sections of the marrow of several of the vertebrae and a rib showed a diffuse massive cellular proliferation strongly suggestive of a malignant process. It had resulted in almost total replacement of the marrow fat and had caused narrowing and atrophy of the bony trabeculae. The proliferation formed no structural pattern and the cells were relatively uniform in size and appearance. They had round, oval, reniform, or lobate nuclei, generally vesicular but occasionally in mitotic division. The cytoplasm was prominent, acidophilic, nongranular, and at times irregular in outline. The vascular spaces were for the most part obliterated. Megakaryocytes were seen infrequently. Small nests of erythropoietic and myeloid tissue were occasionally encountered. There was no necrosis or inflammatory reaction.

Miscellaneous: Sections of the thyroid, aorta, gastro-intestinal tract, pancreas, bladder, prostate, adrenals, and testis showed heavy intravascular and perivascular collections of monocytic cells, many of which appeared immature. None of these tissues showed evidence of a tuberculous reaction.†

DISCUSSION

The combination of the clinical and hematologic features of the reported case stimulated a vigorous controversy among the several attending physicians and consultants which was not completely settled by the results of the postmortem examination. One group interpreted the hematologic findings to be those of a leukemoid reaction complicating a tuberculous infection. This interpretation was

* Two guinea-pigs, inoculated with an emulsion of lymph node, contracted tuberculosis.
† Tubercle bacilli could not be demonstrated in sections of liver, spleen, and bone marrow.
based upon several factors: 1. the known tuberculous infection of the patient, proven bacteriologically, several years before the terminal illness; 2. clinical evidence of activity of the tuberculosis indicated by the pleurisy with effusion and the pericarditis; 3. the specific mobilizing effect of the tubercle bacillus on the monocytes; 4. the occurrence of leukemoid reactions in tuberculosis. Indirectly the rarity of monocytic leukemia strengthened the leukemoid position.

The contrary opinion regarded the hematologic findings as specifically diagnostic of monocytic leukemia.

After a review of the clinical, hematologic, and postmortem findings several considerations led us to exclude a leukemoid reaction in spite of the fact that an active and extensive tuberculous infection not only existed but contributed to the death of the patient.

In general, leukemoid reactions represent alterations in the blood picture, usually the result of an infectious process. Unusually high leukocytosis and the appearance of immature leukocytes in the blood smear may simulate leukemia but, as a rule, repeated competent hematologic study can differentiate such reactions from leukemia. Pathologically one rarely encounters cases, adequately studied postmortem, in which differentiation offers any serious difficulty. The massive hyperplasia and anaplasia of the hematopoietic tissues in leukemia and the widespread cellular infiltrations of viscera are characteristic and specifically diagnostic. Admittedly rare cases are seen in which absolute differentiation between genuine leukemia and leukemoid reactions is not possible even after thorough postmortem study. We do not consider our case to belong in this category.

It is well known that elevation in the percentage of monocytes in the blood may occur in tuberculosis and that these cells are the most typical and characteristic in the inflammatory response of the host tissues. To our knowledge a monocytic reaction of the blood similar to, or even closely approaching, that of our case has never been described in tuberculosis or any other infectious disease. Leukemoid reactions are rare in tuberculosis and they are predominantly of myeloid type, rarely lymphatic. In respect to monocytic reactions in infectious processes, Evans states, "Descriptions of prolonged monocytosis of significant proportion and more particularly of all stages in the life cycle of the monocyte are not available." The presence of promonocytes and blast forms in our case adds considerable weight to the leukemic interpretation.

The few reported cases of leukemia complicating tuberculosis are almost invariably of myeloid or lymphatic type. This is consistent with expectations based upon the relative frequency of the three major types of leukemia and is probably a reflection of an accidental association of the two presumably unrelated diseases. One cannot exclude the possibility, however, that the tuberculous infection may have stimulated an irreversible hyperplasia of the reticuloendothelial cells, i.e., monocytic leukemia. Kirshbaum and Preuss reported co-existent tuberculosis in 13 per cent of 123 cases of leukemia of all types studied postmortem. We have encountered in the literature only one case of active tuberculosis associated with monocytic leukemia.

We consider all of the criteria requisite for the diagnosis of monocytic leukemia
MONOCYTIC LEUKEMIA AND TUBERCULOSIS

to have been fulfilled in our case. These criteria include: 1. the progressive elevation of the white blood cell count, exceeding 100,000 per cu. mm., with monocytes and immature forms of the monocytic series constantly present in high percentage; 2. the character of the reaction of those lymph nodes which were free of tuberculosis; 3. the massive cellularity and anaplasia of the bone marrow; 4. the widespread intravascular aggregates and the heavy perivascular and interstitial infiltrations of monocytic cells in viscera uninvolved by the tuberculous process.

Clinically the rapid course of the illness was typically that of monocytic leukemia resulting in death about two months after the onset of symptoms. The absence of the gingival lesions frequently ascribed to monocytic leukemia is consistent with the experience of Watkins and Hall.

In our opinion the failure to study the supravital staining reaction of the monocytes of the blood does not render their identity questionable. In the blood smears the majority of the cells were morphologically typical monocytes, and transition stages between mature and blast forms were distinct. Of interest in this respect is the fact that there was complete unanimity of opinion among the numerous hematologists and pathologists who studied the blood smears that the cell in question was a monocyte. The characteristic appearance of the cells in the tissue sections also indicated their monocytic nature.

The possibility that the patient terminally developed acute hematogenous dissemination of the tubercle bacilli, and that the widespread perivascular and interstitial monocytic infiltrations of the viscera were early cellular reactions to the bacteremia, has been considered. However, the general character of the cellular infiltrations, and the absence of both focal necroses and the various developmental stages of miliary tubercles in the viscera, so typical of tuberculous bacteremia, negate such a possibility.

SUMMARY

A case of monocytic leukemia associated with active tuberculosis of pleura, pericardium, and lymph nodes is reported.

The criteria for the diagnosis of monocytic leukemia and the factors excluding a leukemoid reaction are presented.

The rarity of monocytic leukemia in contrast with the frequency of tuberculous infections and the rarity of active tuberculosis in the reported cases of monocytic leukemia indicate that the association of the two diseases is probably coincidental.

Grateful acknowledgment is due to Miss Anne Shiras and Mortimer Cohen, M.D., for the photomicrographs.

REFERENCES


ELWYN L. HELLER AND CHARLES H. HILES

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