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GENERALIZED RETICULAR CELL SARCOMA OF LYMPH NODES ASSOCIATED WITH LYMPHATIC LEUKEMIA *

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Leukemia, or even a leukemoid blood picture, is an unusual occurrence in the course of tumors. When the cells in the blood are morphologically identical with those of the tumor, a genetic relationship between the blood picture and the organ changes is generally assumed. If (less frequently) the leukemic cells are of entirely different structure from those of the tumor, a relationship is less firmly established. In every instance the interpretation is difficult, and the diagnosis frequently in doubt.

The case which forms the basis of this communication is one in which lesions thought to be those of an unusual tumor of the lymphatic apparatus, are associated with those of lymphatic leukemia.

REPORT OF CASE

Clinical History: W. H., Shipping clerk, age 46 years. Entered Bellevue Hospital June 14, 1926, complaining of swelling on the left side of neck, duration seven weeks.

Family History and *Past Personal History:* Irrelevant.

Present Illness: Seven weeks ago the patient noticed a swelling on the left side of the neck which increased gradually in size. It was not painful. The patient had occasional pains in the epigastrium and suprapubic regions, of short duration, which had no relation to meals, defecation or exertion. He had lost a great deal of weight in the last two months.

Physical Examination: (Positive findings only.) Adult white male, appears chronically ill. Marked emaciation. Eyes: Petechial hemorrhages in palpebral conjunctivae. Neck: Masses of nodes in left cervical region, anterior and posterior chains. The individual nodes appear to be about 2 cm. in diameter. There are smaller ones in both supraclavicular regions. The nodes are firm and

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apparently discrete. Abdomen: Distended. Spleen edge 10 cm. below costal margin, firm, surface feels nodular. Liver edge at level of umbilicus, hard, smooth. Lymph nodes: Cervical, axillary, epitrochlear, inguinal, all enlarged, firm, discrete, not tender.

Blood Examination: Red blood count, 3,700,000; hemoglobin 60 per cent; white blood count 98,400; polymorphonuclear neutrophiles 7 per cent; eosinophiles 0.2 per cent; lymphocytes 90 per cent; monocytes 2 per cent; myelocytes 0.6 per cent; plasma cells 0.2 per cent. There are many degenerated white cells in the smear. There is slight anisocytosis and pallor of the red cells.

Clinical Diagnosis: Lymphatic leukemia.

Course in Hospital: Progressive, downward. Died July 6, 1926.

Necropsy

B. H. No. 11643. Summary of positive findings. There is generalized lymphadenopathy. The abdominal nodes form a retroperitoneal mass which extends from the diaphragm to the pelvis and from spleen to right kidney. The mass is composed of nodes which are 0.2 to 8 cm. in diameter, mostly discrete. Nodes in the mesentery and groin, cervical and axillary regions are also enlarged. On section all are very soft. Some are white or gray, some mottled with red, a few definitely hemorrhagic in whole or in part. Some nodes have central areas of the same consistency, but of canary yellow color. None is necrotic.

Spleen: 23 by 15 by 10 cm. Capsule is smooth, surface coarsely nodular. On section, there are numerous white, gray or yellow nodules measuring up to 2 cm. in diameter, of the same consistency as the lymph nodes. Many of these nodules have a hemorrhagic periphery, some have canary yellow centers. There is recent infarction.

Liver: Enlarged. Weight 2660 gm. It is pushed to the right and rotated by the peritoneal mass so that the left border is near the midline. There are numerous white spots on section, most less than 0.1 cm. in diameter, but some measuring up to 1.5 cm.

The nodules in the liver and spleen have the same appearance and consistency as the lymph nodes.

Intestine: In the ileum is a small ulcer, about 0.5 cm. in diameter, involving only the mucous membrane. It appears to be directly over a lymphoid follicle in the submucosa.

Bone Marrow of Rib: Hyperplastic, grayish red.

Bones: Normal, except for a fibroma of the periosteum on dorsal vertebra, 6.5 cm. in diameter.

Microscopic Examination

Lymph Nodes: None of the lymph nodes examined is normal. Two types of histological lesions are observed:

(*A*) The general architecture of the node is preserved. The lymphoid tissue is markedly hyperplastic. The normal distinction between follicular and medullary areas is lost, the whole being overrun with lymphocytes, forming large areas separated by trabeculae. There are no germinal centers.

The cells are nearly all lymphocytes of the small variety. Only a few large lymphoid cells are seen. Mitoses are present, but not common.

The blood and lymph channels contain an abnormally large number of small lymphocytes. The surrounding fat tissue is infiltrated with the same cells. The endothelium and reticular tissue are normal.

(*B*) In the other type of lesion, there are numerous polymorphous "endothelioid" cells, sometimes closely packed, more often loosely arranged, which have the following characteristics:

The cells are several times as large as the lymphocytes. Their nuclei are large and vary in shape. Hypertrophied forms and giant cells with nuclei resembling those of megakaryocytes are present in very variable numbers.

The nuclei have definite membranes, several prominent nucleoli, and a fine chromatic network.

The cytoplasm is abundant, often with protoplasmic processes. It is moderately basophilic, particularly with the basic blue stains, less so with hematoxylin. It is finely granular, but no special leukocytic granules are present. The benzidine peroxydase reaction in these cells, as in the lymphocytes, is negative.

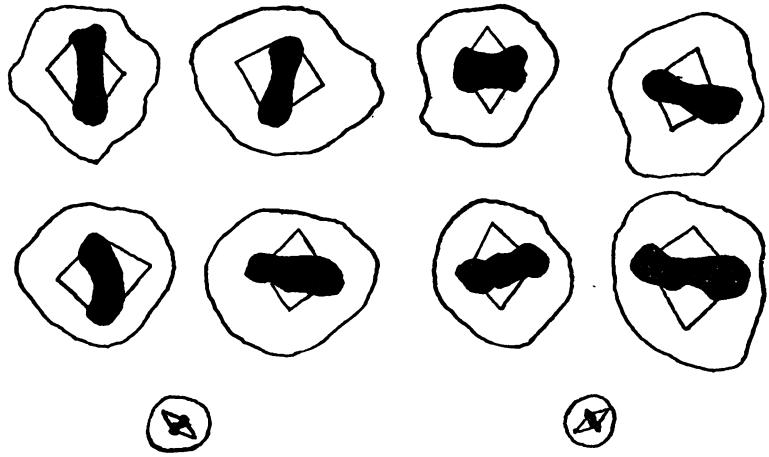
An interesting and occasional very conspicuous cytoplasmic constituent is the centrosome, which is distinctly stained, particularly by phosphotungstic acid hematoxylin (black), and by azure-eosin (red). This structure is single or double, sometimes multiple. From the centrosome are radiating lines (astral rays) which, under suitable resolution, appear granular.

The centrosome and astral rays are present not only in dividing cells, but also in many at rest. The centrosome, in cells with indented nuclei, is sometimes situated just within the nuclear indentation, or

in the cytoplasm on the same side of the nucleus. If the cell has cytoplasmic processes a centrosome may often be seen in each process if the angles are included in the plane of section. In dividing cells, a centrosome is situated in each mitotic angle.

The angle of mitosis is, on the average, 84° (Text-Fig. 1).

These cells are obviously of connective tissue origin, though the cells from which they arise can be determined with neither ease nor accuracy. They seem to have no genetic relationship with the



TEXT-FIG. 1. Mitoses in tumor cells and in lymphocytes, showing characteristic variations in the mitotic angles. The two small cells are lymphocytes, the others are from the tumor. Camera lucida sketch.

lymphocytes. No conversion of lymphocytes into the polymorphous cells, or vice-versa, could be found, although the two lesions are frequently found together. Neither is there any definite evidence of their origin from endothelium. Frequently they are seen just outside the lymph vessels, with intact endothelium between them and the lumen. Often, also, they are found in the situation where lymph sinuses ordinarily would be found.

I am inclined to regard these polymorphous, "endothelioid" cells as arising from the reticulum, particularly that part known as reticulo-endothelium, in the lymph nodes.

The two types of lesions are found in all the groups of nodes examined, almost always in the same nodes. Only occasionally is a section seen with only one lesion, *i.e.*, purely leukemic, or purely neoplastic. Sections through two adjacent nodes may show an

abrupt change from a leukemic to a neoplastic lesion, not an extension from one node to another.

Liver: The liver has the same two types of lesions that are found in the lymph nodes: leukemic and neoplastic.

The leukemic lesion consists of periportal lymphomata of different sizes, and smaller intralobular lymphocytic collections. These lesions are identical with those usually seen in lymphatic leukemia.

The other lesion consists of tumor nodules of the same cell type described in the lymph nodes, which form large areas completely destroying the liver tissue, and infiltrating the surrounding liver lobules. Sometimes these tumor cells are seen in the center of a leukemic collection, especially in the vicinity of a large tumor mass, but no transitions between the two cell types can be identified.

Spleen: The nodules observed in the gross specimen are composed of collections of the same type of cell described in the lymph nodes and liver as "tumor cells." These collections are mainly rather compact, completely destroying and replacing the splenic tissue. Smaller collections of the same type of cells are present in the splenic pulp.

The malpighian corpuscles are not observed, the remaining splenic tissue consisting of numerous small lymphocytes scattered without definite arrangement.

Intestine: The small ulcer is directly over a nodule in the submucosa which evidently was a lymphoid follicle. Only a small portion of the lymphoid tissue is present, the remainder being obliterated by tumor cells identical in appearance with those described above. The main mass of the tumor is confined to the follicle, but a few tumor cells can be seen infiltrating the mucosa. The remaining lymphoid tissue is too small in amount to determine whether or not it is the seat of leukemic change.

Kidney: There is hyaline degeneration of the tubular epithelium. In a few areas are poorly defined collections of small lymphocytes.

Tumor of Periosteum: This consists of closely packed, elongated fibroblasts and collagen fibers arranged in bundles which run in different directions. The cells have no resemblance to either the lymphocytes or to the cells of the generalized tumor. In a few places there are collections of small lymphocytes.

Bone Marrow: Unfortunately, examination of the marrow was confined to that of the ribs and vertebrae. In those situations, the marrow is very cellular, the predominating cell type being the small

lymphocyte. In a few areas, small clusters of myeloid cells remain. The picture is regarded as typical of the marrow in chronic lymphoid leukemia. Tumor cells were not observed.

My interpretation of this case is as follows:

The patient had chronic lymphatic leukemia for a much longer time than the history indicates. Subsequently there developed a rapidly growing, malignant tumor arising from reticular and reticuloendothelial cells of the lymphoid tissues. The tumor developed in, encroached upon, and destroyed tissue which was previously the seat of leukemic changes.

Epicrisis

On the Leukemic Lesion: It is known that blood pictures resembling leukemia may occur as a result of different conditions, among them tumors. It is also known that in cases with the gross and microscopic lesions of leukemia, the blood picture may give no indication of this condition. We must, therefore, regard the blood picture in leukemia (or in any other condition) as a *symptom* which may vary within wide limits and which does not in any sense constitute the disease itself. A diagnosis of leukemia based solely on the blood picture may, therefore, be questioned, but when combined with the typical features of leukemia in the various organs, it must be regarded as established.

In other words, the diagnosis of leukemia rests, in the final analysis, on tissue changes without which the disease cannot be said to exist, regardless of the blood findings. When these changes are present, leukemia may be diagnosed regardless of the apparent cause, for we are not able at present to establish the diagnosis of leukemia on an etiological basis.

Applying these statements to the present case, we may diagnose the presence of leukemia because of the typical histological changes in the organs together with a leukemic blood picture. Whether the leukemia is due to the tumor or is a disease *sui generis*, is another question.

On the Tumor: There can be little doubt that the lesion described in the foregoing account as a "tumor" should be so considered. The classification of the tumor, however, presents greater difficulties.

Although arising primarily in lymphoid tissues, the tumor is composed neither of lymphocytes nor their immediate precursors.

This is borne out by a study of the cells in both section and smear preparations, in neither of which do the tumor cells resemble any variety of normal blood corpuscles or their formative cells. For this reason, I think the term "lymphosarcoma" is not applicable.

The tumor is apparently derived from reticular and reticulo-endothelial cells. It has no connection with ordinary vascular endothelium, and is therefore not an "endothelioma." Certain properties normally possessed by reticulo-endothelium, however, are missing. For example, the cells do not produce reticulum fibers. In silver impregnation methods, an increase in the amount of reticulum is not demonstrated, nor is there a very intimate relation between cells and fibers. Phagocytosis is not observed, and abnormal cytoplasmic inclusions are not found in the tumor cells. This, however, does not disprove their origin from reticulo-endothelium, as it is known that tumor cells do not necessarily carry on the functions of the tissue from which they arise.

It would appear, therefore, that we are justified in regarding the lesion *in its final state* as a tumor probably arising from reticulum cells. Although it cannot be proved that the lesions in their incipiency were of the same nature as those observed at necropsy, nevertheless to postulate a preëxisting lesion of another type (which has been transformed), is to read into the picture signs which are not there.

On the Relation of Leukemia to Tumor: The two lesions in this case have been referred to as "leukemia" and "tumor" for purposes of description. The fact that leukemia may itself be a tumor, does not enter into this discussion.

It is possible that the development of one of the lesions was dependent on the existence of the other. This question, however, involves a discussion of the etiology of both leukemia and tumors, and cannot be elaborated here. There is nothing in the foregoing account that precludes such dependence, and the fact that the tumor was encroaching on tissues formerly the site of leukemic changes, points in that direction.

The complete independence of the two lesions is conceivable, but not susceptible of direct proof. On one point, however, the histological evidence is conclusive: there is no evidence of the transformation of the cells of one lesion into those of the other. Lymphocytes and tumor cells, although intimately intermingled, are morphologic-

ally distinct. Cells in the blood stream are identical with those of the leukemic lesions, but strikingly different from the tumor cells.

This difference is also seen in a study of the "mitotic angles" of dividing cells. Ellermann [1] has observed that cells in mitosis have mitotic angles characteristic of the cell type. Petri [2] has confirmed this, and has used the mitotic angle to differentiate cell types in leukemia. Thus myeloblasts have angles of about 66° to 70°; neutrophil myelocytes about 68° to 70°; erythroblasts 21° to 22°; lymphocytes about 45°. Measurements of the mitotic angles of cells in this case showed that in lymphocytes the angle is about 45°, but in the tumor cells, 84°. There is considerable variation among the different cells of the tumor, and individual angles were found to vary from 69° to 108°, but none was found to be as low as in the lymphocytes. The average angle observed in the tumor does not correspond to any reported in blood cells.

That this case is not a "leukemic transformation" of another condition is evident from a study of the sections, which indicates that the leukemia was probably the lesion first to develop. At the time of death, the tumor was much the more actively growing lesion. The wide distribution but relative quiescence of the leukemic lesion indicates long existence and slow development.

The evidence presented by the microscopic preparations thus enables one only to diagnose the *presence* of two lesions, without giving any definite indication that they are genetically related.

I am indebted to Dr. Francis Carter Wood for the photomicrographs illustrating Figs. 3 to 8, inclusive.

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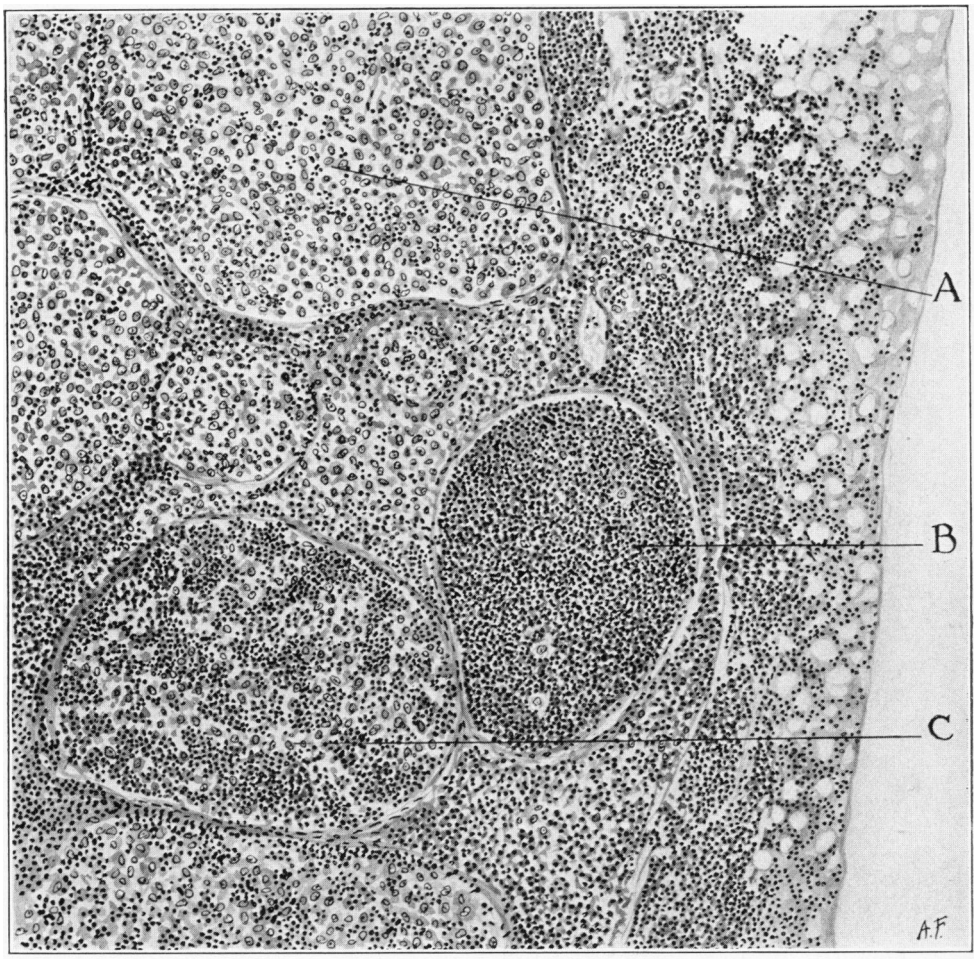
1. Ellermann, V. Messung der Mitosenwinkel als Methode zur Unterscheidung verschiedener "lymphoider" Zellformen. *Folia Haematol.*, 1923, xxviii, 207.
2. Petri, Svend. Histologische Untersuchung eines Falles von myeloischer Leukämie mit Messung der Mitosenwinkel. *Folia Haematol.*, 1926, xxxii, 103.

DESCRIPTION OF PLATES

PLATE 70

FIG. 1. Lymph node. (A) area of almost complete replacement by tumor; (B) remains of leukemic lesion; (C) partial replacement of leukemia by tumor.

FIG. 2. Lymph node. Higher magnification of a tumor area.



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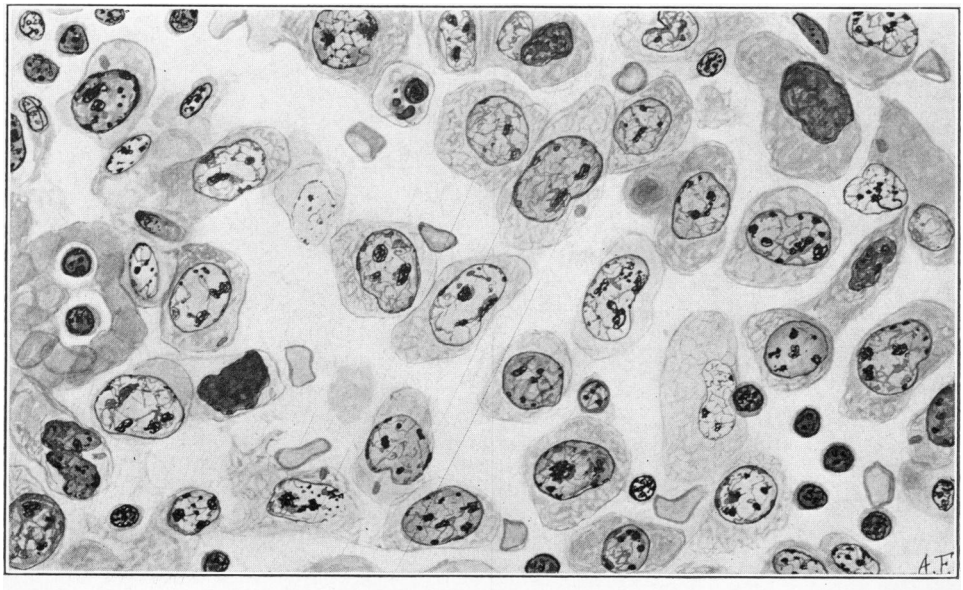

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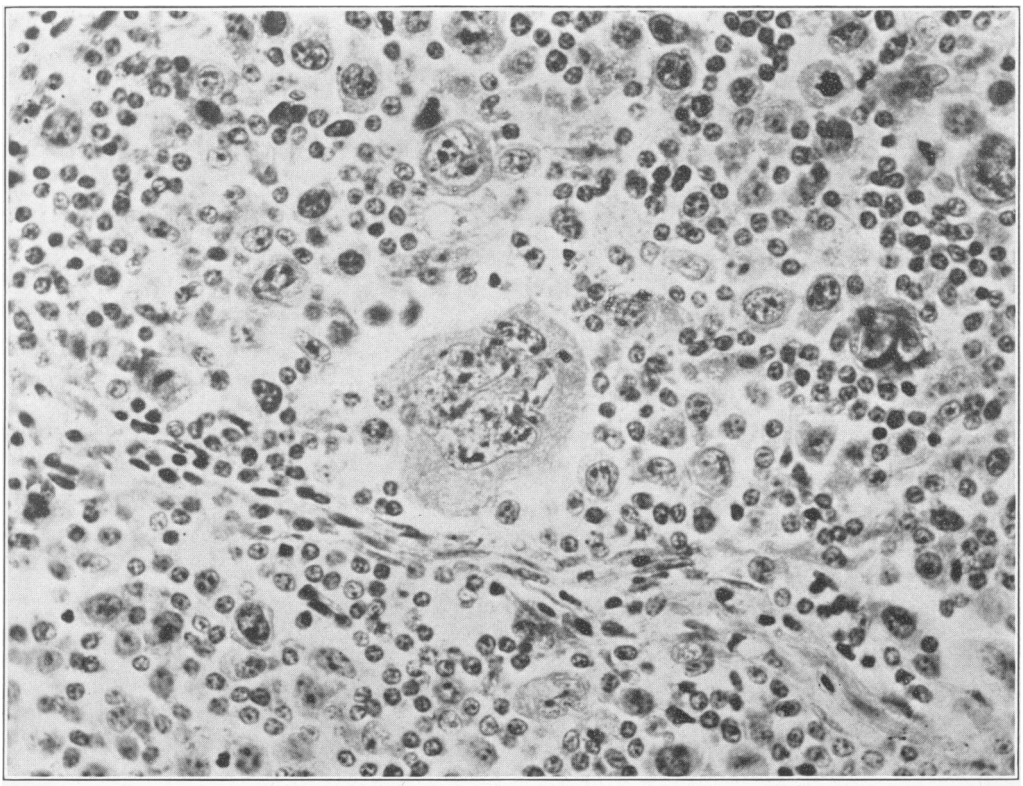
Richter Reticular Cell Sarcoma and Lymphatic Leukemia

PLATE 71

FIG. 3. Lymph node. A tumor giant cell and other tumor cells intermingled with lymphocytes. × 500

FIG. 4. Liver. Edge of a tumor nodule. (A) tumor cells; (B) liver cells; (C) collections of leukemic cells (lymphocytes) in the capillaries. × 500



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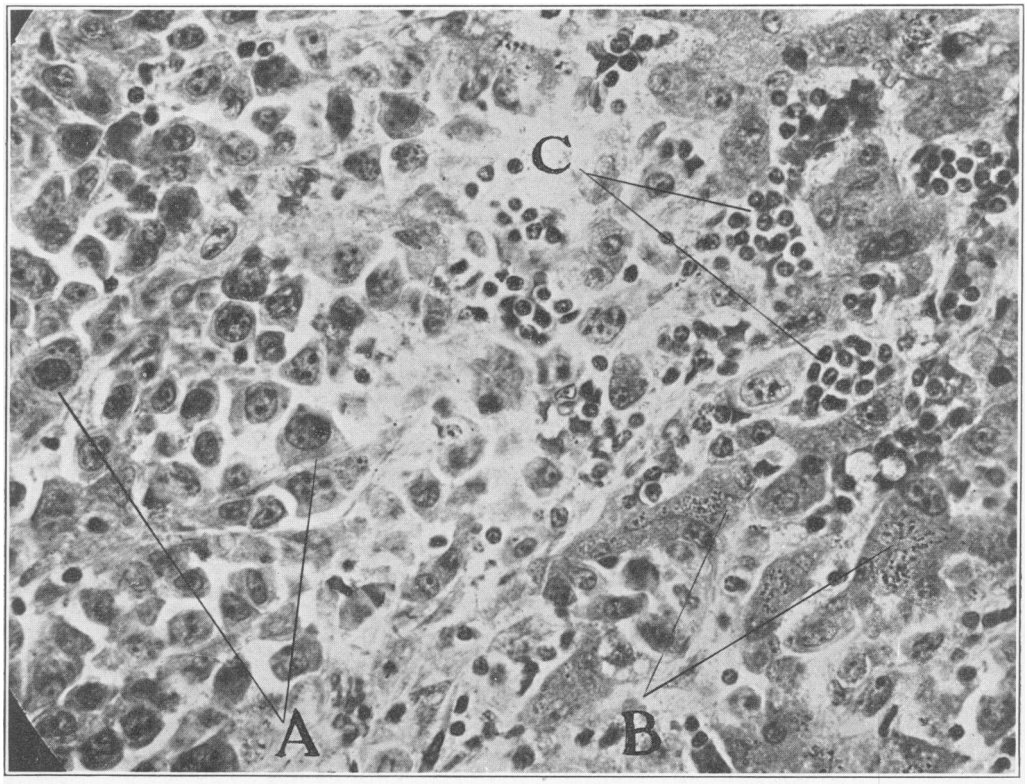

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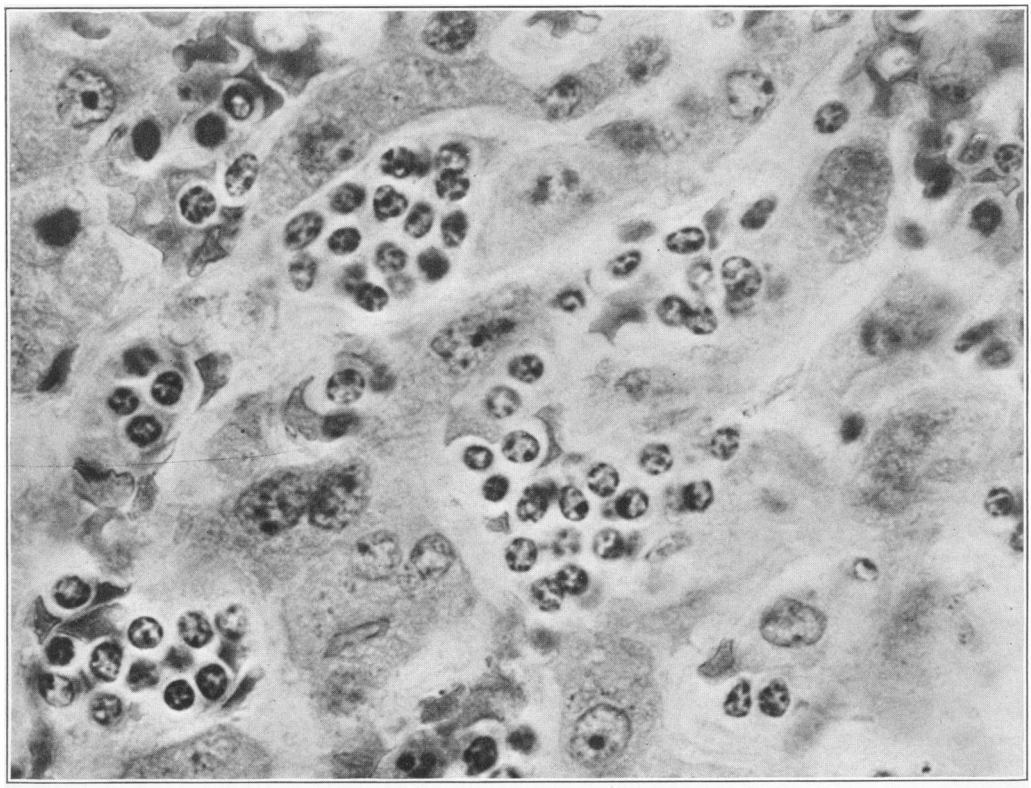
Richter Reticular Cell Sarcoma and Lymphatic Leukemia

PLATE 72

FIG. 5. Liver. A higher magnification of the leukemic collections. × 1000

FIG. 6. Liver. A portion of the tumor under the same magnification as Fig. 5. Compare the size and structure of tumor cells and lymphocytes. × 1000



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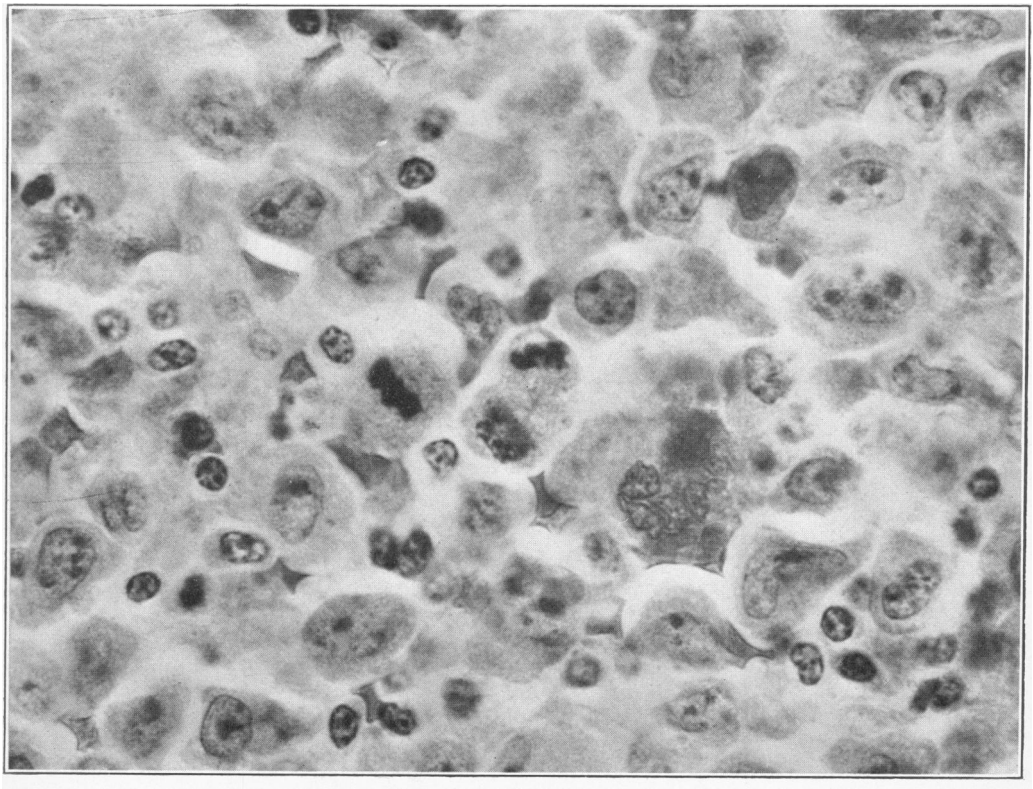

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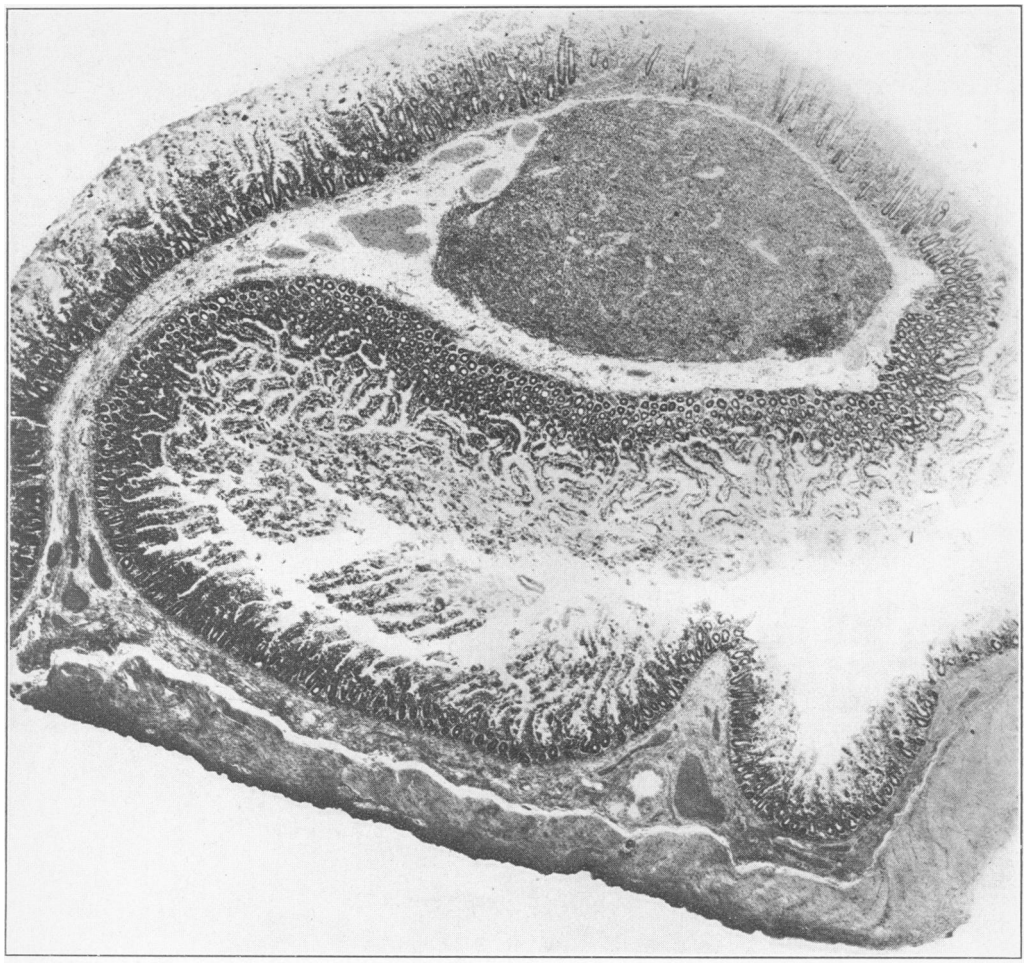
Richter

Reticular Cell Sarcoma and Lymphatic Leukemia

PLATE 73

FIG. 7. Intestine. Submucous nodule composed of tumor cells. × 20.

FIG. 8. Lymph node. Stained for reticulum fibers.



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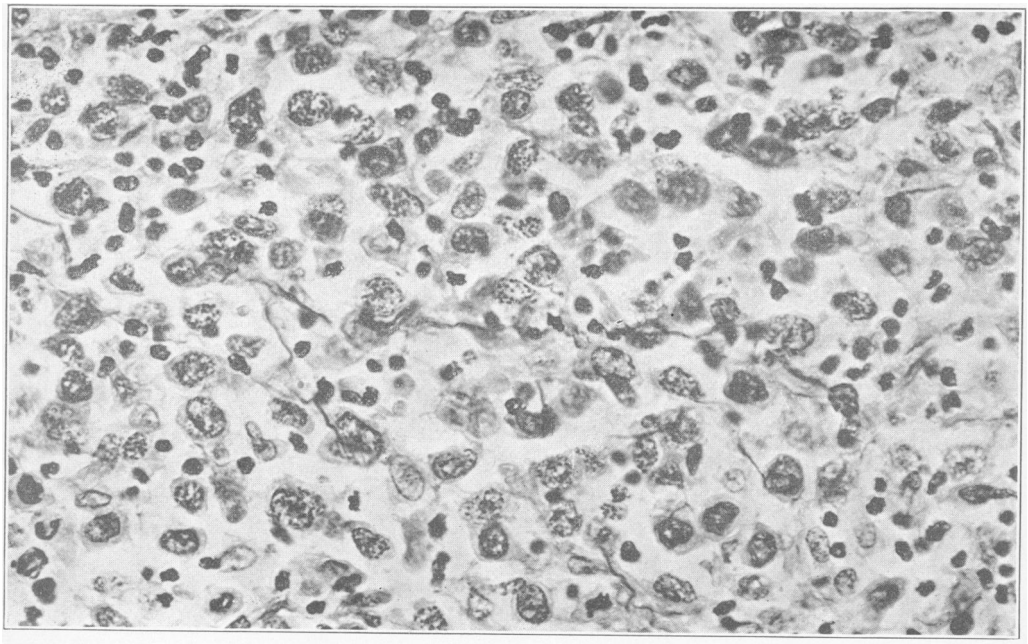

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Richter Reticular Cell Sarcoma and Lymphatic Leukemia