ANIMAL MODEL OF HUMAN DISEASE

Large Granular Lymphocyte Leukemia in F344 Rats

Model for Human Tγ Lymphoma, Malignant Histiocytosis, and T-Cell Chronic Lymphocytic Leukemia

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Biologic Features

Large granular lymphocyte (LGL) leukemia, or mononuclear-cell leukemia, is a spontaneous neoplasm arising in the spleen which occurs in 10–35% of Fischer rats over 18 months of age.[1,2] The clinical illness lasts for several weeks and is characterized by depression, weight loss, palor, icterus, and a palpably enlarged spleen. Affected rats invariably die. The gross pathologic features include severe splenomegaly, a pale mottled liver (Figure 1), variable enlargement of visceral lymph nodes, and petechial hemorrhages in lungs, brain, and lymph nodes.[2] Histologically, there is diffuse infiltration of splenic red-pulp sinusoids with tumor cells, lymphoid depletion of splenic follicles, and erythrophagocytosis by tumor cells (Figure 2). The liver has sinusoidal infiltration by tumor cells, some portal infiltration, and severe centrilobular hepatocellular necrosis. Lymph nodes have sinusoidal, infiltration to diffuse obliteration of architecture by tumor cells. Bone marrow is infiltrated in less than one-half of the cases. There is marked myeloid hyperplasia and medullary osteosclerosis in the long bones. Lungs characteristically have numerous, small tumor-cell nodules in alveolar septa. There is occasionally widespread perivascular and lymphatic infiltration of many tissues.[2] Leukocyte counts range from 5 to 370 $\times$ 10^3 cells/μl. Leukemic rats consistently have immune-mediated hemolytic anemia (Figure 3), thrombocytopenia, and clotting abnormalities suggestive of disseminated intravascular coagulation.[3] Hyperbilirubinemia, increased aspartate and alanine aminotransferases, alkaline phosphatase, lactate dehydrogenase, and decreased serum alpha globulins also accompany the tumor.[4] Tumor cells are pleomorphic, with round to reniform nuclei and abundant basophilic cytoplasm (Figure 3) containing distinct red granules. There is a variable expression of β-glucuronidase, acid phosphatase, and napthol AS-D acetate esterase, which is NaF-sensitive.[5,6] The cells have Fc receptors, are variably adherent, possess a low capacity for phagocytosis *in vitro*,[6] and have natural killer (NK) cell activity.[5] Surface antigen profiles demonstrate tumor cells consistently positive for the thy 1.1, M1/70, OX-8, and Asialo GM_1 antigen,[5] consistent with normal rat LGL.[7] Isogeneic transplantation is consistenly successful and reproduces all of the associated clinicopathologic features.[8]

Comparison With Human Disease

Chronic leukemias of T-cell origin (TCLL) are a heterogeneous group of disorders with variable clinical, pathologic, cytologic, and immunologic expression. Some cases of T-cell chronic lymphocytic leukemia have been characterized by cells compatible with LGLs which

Publication sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and supported by Public Health Service Grant RR-00301 from the Division of Research Resources, National Institutes of Health, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

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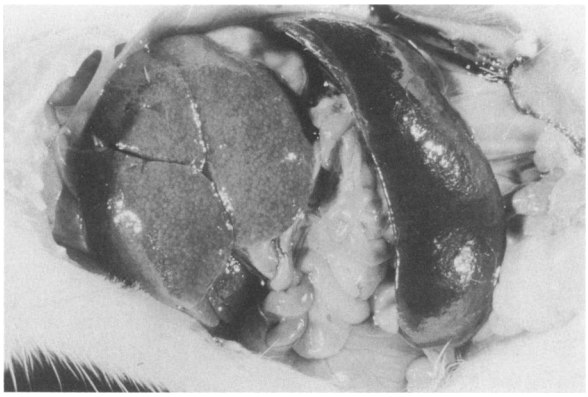

Figure 1—Young F344 rat with transplanted large granular lymphocyte leukemia of 7 weeks' duration. There is splenomegaly and hepatocellular necrosis.

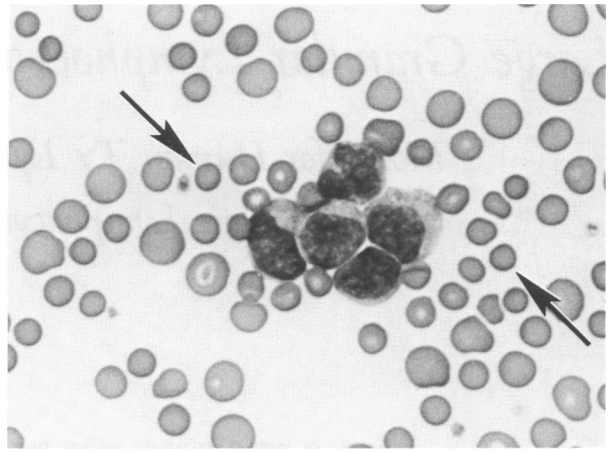

Figure 3—Peripheral blood smear with tumor cells, spherocytes (*arrows*), and anisocytosis. (H&E, ×650)

expressed NK activity.[9,10] Human LGLs make up the majority of the two subsets of peripheral blood mononuclear cells called Tγ cells and third-population cells. These cells are morphologically, biochemically, and functionally similar to LGLs in rats.

Tγ lymphoma and malignant histiocytosis have very similar pathologic features and may share a common stem cell which is similar to the LGL.[11,12] Clinically, patients may have weight loss, fever, hepatosplenomegaly, and jaundice, with variable lymphadenopathy. Malignant histiocytosis is characterized by diffuse infiltration of splenic red pulp sinusoids by an erythrophagocytic histiocytic tumor cell and lymphoid depletion of white pulp.[13] The liver has portal as well as sinusoidal infiltration by tumor cells. The lymph nodes retain normal architecture in early involvement with diffuse infiltration and expansion of sinusoids by "atypical histiocytes." In advanced disease, there is obliteration of nodal architecture and infiltration of the capsule and surrounding tissues. Interstitial pulmonary infiltrates may be observed radiographically. Associated clinical abnormalities include hyperbilirubinemia, increased alkaline phosphatase, and aminotransferases,

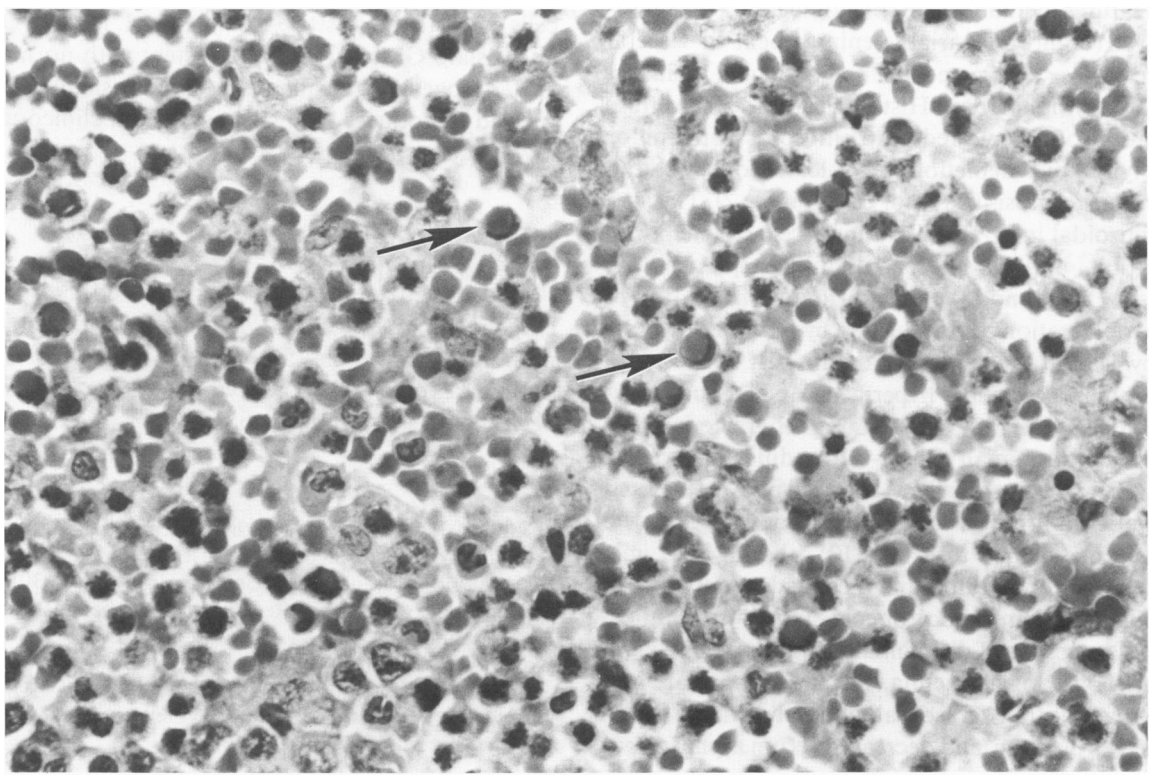

Figure 2—Spleen with diffuse sinusoidal infiltration by neoplastic large granular lymphocytes and erythrophagocytosis by tumor cells (*arrows*). (H&E, ×650)

Coombs' positive and negative hemolytic anemia, and clotting abnormalities.[13,14] There is a variable leukemia, featuring histiocytic cells often positive for acid phosphatase and nonspecific esterase. Erythrophagocytic Tγ lymphoma has similar characteristics, including thrombocytopenia.[12] Cells from this tumor were positive for acid phosphatase but negative for esterase. The occurrence of skin infiltrates in some human cases has not been observed in LGL leukemia of rats.

The relationship of these neoplasms ultimately depends upon identification of cell type. The reported variability in morphology, cytochemistry, and function might easily reflect stages of differentiation by different clones of transformed cells. Such heterogeneity has been shown even in the LGL tumor of isogeneic Fischer rats. Development of surface antigen profiles by flow cytometry for a series of these pathologic entities and comparison with differentiation antigens on human leukocytes are needed before these neoplasms can be completely classified. However, the large granular lymphocyte, appears to occupy an important position in the characterization of T-cell leukemias.

Usefulness of the Model

Besides serving as a model for T-cell leukemias, LGL leukemia should provide investigators with abundant cells for the studies of certain aspects of LGL and NK-cell function. In addition, it is an excellent, reproducible model of tumor-induced autoimmunity. The ease of handling, high frequency of successful transplantation, and short latency period mark it as a convenient system for use.

Availability

Fischer 344 rats are widely available from a large number of commercial laboratory animal producers.

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