Proliferative Lesions of the Hematopoietic and Lymphatic Systems in Rats


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INTRODUCTION

Terminology used to describe hematopoietic neoplasms in rats is quite varied. Many investigators simply refer to hematopoietic neoplasms as lymphomas, leukemias, or lymphoreticular disease (2, 3, 6, 16, 27, 41). Since the rat has the potential to be an excellent immunomorphologic model for human lymphoproliferative diseases, proper diagnosis and characterization of proliferative hematopoietic lesions is important. This manuscript presents a biologically accurate morphologic classification of proliferative lesions in the rat.

FIXATION OF LYMPHOID TISSUES

Hematopoietic tissues are commonly fixed in 10% neutral buffered formalin. This procedure is satisfactory for light microscopy. However, if the investigator anticipates the use of immunocytochemistry, special procedures or fixatives may be necessary. Cell surface antigens and immunoglobulins may require frozen sections or Bouin’s, B-5, or Zenker’s fixation. Enzyme digestion with trypsin or another protease may enhance immunoreactivity of antigenic determinants in formalin-fixed rodent tissue.

APPLICATION OF IMMUNOCYTOCHEMISTRY FOR DIAGNOSIS OF HEMATOPOIETIC NEOPLASMS

Immunocytochemistry can serve as a valuable adjunct in diagnosing hematopoietic neoplasms in rats, especially in paraffin-embedded tissues. Specific antigens may be localized in cells and tissues, and the immunoreactivity of polyclonal and monoclonal antibodies to these antigens provides a more accurate basis of tumor diagnosis and aids in understanding the pathogenesis of these neoplasms. Both specific and nonspecific staining patterns may be focal or diffuse and may be categorized by localization as tissue, nuclear, cell membrane, nuclear membrane, cytoplasmic-diffuse, cytoplasmic-focal, or granular, whole cell (nuclear, cytoplasmic, and extracellular) (7). Table 1 may be useful for determining the proper procedure to use.

MORPHOLOGY

NON-NEOPLASTIC LESIONS

SPLEEN

Hyperplasia, Red Pulp (Figures 1-3)

Hyperplasia of the red pulp (hematopoiesis) is a normal finding in spleens of young rats. Splenic hematopoiesis may increase in response to stimuli (reactive

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### Table 1

**EXAMPLES OF THE LOCALIZATION OF IMMUNOCYTOCHEMICAL STAINING PATTERNS IN HEMATOPOIETIC NEOPLASMS IN RATS**

<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>Selected Antigens</th>
<th>Localization of Staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Cell Lymphomas (FCC Lymphoma, Immuno-……..Immunoglobulins.............................Cytoplasm</td>
<td>(IgA, IgG, IgM, etc.)</td>
<td></td>
</tr>
<tr>
<td>T Cell Lymphoma (Lymphoblastic) ....................OX-7, OX-8, OX-19, ......................Cell Surface</td>
<td>W3/25, W3/13</td>
<td></td>
</tr>
<tr>
<td>LGL Lymphoma (Leukemia) ..........................OX-8 .....................................Cell Surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytic Leukemia ................................Lysozyme .................................Cytoplasmic Granules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythroleukemia .....................................Hemoglobin ..................................Cytoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basophilic Leukemia ................................Lysozyme ..................................Cytoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histiocytic Sarcoma ..................................Lysozyme; Vimentin; ED-1 ...............Cytoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymoma ........................................Keratin .........................................Cytoplasm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*hematopoiesis* such as anemia, chronic antigen stimulus, thrombocytopenia, or to certain neoplasms. During reactive hematopoiesis, the spleen may enlarge several times and an increase may occur in either the red cells (*erythropoiesis*), white cells (*granulopoiesis*), or megakaryocytes (*megakaryocytosis*) (37). The splenic cords usually are filled with hematopoietic elements in varying degrees of differentiation and frequently the white pulp is atrophied. Reactive hematopoiesis must be distinguished from hemopoietic neoplasia.

Differentiation between reactive granulopoiesis (*myeloid hyperplasia*) and granulocytic leukemia is sometimes difficult. In these cases, cytochemistry, immunocytochemistry, DNA probe techniques, and/or other special techniques may be necessary to determine if the proliferating cells are monoclonal or polyclonal.

**Hyperplasia, White Pulp (Figure 4)**

Hyperplasia of the white pulp may occur in the T-cell zone, the periarteriolar lymphoid sheath (PALS), follicular B-zone, and/or marginal zone (37). Increased numbers of T-cells may be seen in early metastatic thymic T-cell lymphomas and other lymphomas or leukemias. Hyperplasia of the follicular B-zone (*follicular hyperplasia*) occurs in acute and chronic immune responses to antigens and/or administration of certain chemicals.

**Focal Lymphoid/Histiocytic Hyperplasia (Figures 5 & 6)**

Focal lymphoid/histiocytic hyperplasia of the spleen is an uncommon spontaneous lesion which has been described in the Fischer rat (31). The expansile lesion is solitary and may be up to a centimeter in diameter. It consists of a sheet of mature lymphocytes containing scattered clusters of pale staining macrophages. The etiology and pathogenesis are unknown.

**Plasmacytosis (Figure 3)**

Plasmacytosis may be associated with inflammatory, infectious, or neoplastic lesions in other organs. Plasma cells and their precursors are readily distinguishable after staining for immunoglobulins. This lesion often accompanies myeloid hyperplasia.

**LYMPH NODE**

**Hyperplasia (Figure 7)**

In normal rats, lymphoid follicles may be evident to varying degrees, in part dependent on the plane of section of the node, the age of the animal, and its health status (38). Hyperplasia may be either cortical or medullary. During normal response to antigens, the magnitude of B-cell response is indicated by the number and the size of the follicles, development of germinal centers, and the activity of the cells in the follicles. Follicular dendritic cell hyperplasia may also be seen. Hyperplasia of the paracortex may include lymphocytes, large granular lymphocytes, and interdigitating reticular cells.
Plasmacytosis (Figures 8 & 9)

Plasmacytosis is a common finding in the lymph nodes of rats, especially in the mandibular lymph nodes. Plasma cells are located predominantly in the medullary cords. Mature plasma cells have a characteristic purple to intensely eosinophilic cytoplasm, eccentrically located nuclei, and cartwheel-patterned nuclear chromatin. Some cells may contain Russell’s bodies. Plasmacytosis often is seen in lymph nodes draining tissue with lesions caused by infectious agents and tumors.

Sinus Histiocytosis (Figure 10)

Sinus histiocytosis of the lymph nodes is characterized by a predominant population of histiocytes in the sinuses and is frequently seen in lymph nodes draining inflammatory lesions. The abundant cytoplasm of the histiocytes has a distinct eosinophilic appearance and may contain hemosiderin and other phagocytized materials.

Mastocytosis

Mastocytosis is an increase in the number of mast cells in the lymph nodes. The number of mast cells in a specific site may vary from strain to strain. The etiology and pathogenesis are unknown.

THYMUS

Hyperplasia (Figures 11 & 12)

Thymic hyperplasia occurs occasionally in older rats and may involve either the cortex or the medulla. It usually occurs in atrophic thymuses. Thymic lymphoid hyperplasia is characterized by solid populations of small, dark-staining lymphocytes. In some instances this may be the result of an early thymic lymphoma. Epithelial hyperplasia is also common in aging rats and may occur independently or in conjunction with lymphoid hyperplasia. Hyperplastic epithelial cells are paler-staining with more abundant cytoplasm.

BONE MARROW

Hyperplasia

Hyperplasia of the bone marrow may involve an increase in both erythroid and granulocytic cells. The granulocytic component may predominate. The change is usually in response to a systemic stimulus and similar changes are usually also present in the spleen.

Mastocytosis

Mastocytosis is an increase in mast cells that may occur in the bone marrow of older rats. The cause is often unknown.

NEOPLASTIC LESIONS

The authors would prefer not to use the term “leukemia” in the classification of hematopoietic neoplasms with the exception of those of bone marrow origin (myelogenous leukemias); granulocytic leukemia, erythroid leukemia, and basophilic leukemia. Table 2 presents a summary of the cytologic and anatomic features of selected hematopoietic neoplasms described below.

LYMPHOMAS

Follicular Center Cell (FCC) Lymphoma (Figure 13)

FCC lymphoma most commonly involves the spleen, liver, and lymph nodes. Neoplastic cells may range in size from small to large or may be a combination of sizes. Cells are cohesive and the cytoplasm usually is more abundant in larger cells. Nuclei may be cleaved or non-cleaved, and larger cells tend to have vesicular nuclei with prominent nucleoli. Mitotic index generally is low. Tumor cells contain immunoglobulins which can be demonstrated by immunocytochemistry.

Plasma Cell Lymphoma (Figure 14)

Spontaneous plasma cell lymphomas are uncommon. Neoplastic cells are small to large, are non-cohesive, and have abundant amphophilic cytoplasm. Nuclei are round to oval and have irregularly margined, condensed chromatin. Mitotic activity is variable.

Immunoblastic Lymphoma (Figure 15)

The pattern of organ involvement in immunoblastic lymphoma is similar to that of FCC lymphoma, but immunoblastic lymphoma usually is more invasive. Neoplastic cells are large with conspicuous amphophilic cytoplasm; plasmacytoid features may be prominent. The cells are usually non-cohesive, and the nuclei are large and vesicular with multiple, conspicuous nucleoli. Mitotic index is intermediate to high. In the European LOU rat, these tumors arise from Peyer’s patches of the ileocecal junction (28).

Lymphoblastic (Lymphocytic) Lymphoma (Figures 16 & 17)

Lymphoblastic (lymphocytic) lymphoma is more common than FCC lymphoma, but is also relatively rare in the rat (11). The spleen, liver, lymph nodes, thymus, bone marrow, and kidneys are commonly involved, and leukemia often occurs. Neoplastic cells vary in size but tend to be uniform and non-cohesive. Cytoplasm is scant and nuclei are round and often contain multiple prominent nucleoli. Mitotic index is intermediate to high.
Large Granular Lymphocyte (LGL) Lymphoma (Leukemia) (Figures 18-25)

Large granular lymphocyte (LGL) lymphoma is characterized grossly by splenomegaly (35), and was initially characterized as mononuclear cell leukemia. Neoplastic cells are small but pleomorphic and contain round or irregular nuclei often eccentrically located in the cell (33). Nuclei are round with either uniform or irregular nuclear membranes, coarsely clumped and margined chromatin, and a single small nucleolus (32, 34). Tumor cells are OX-8 immunoreactive and antibodies to granule antigens such as serine esterase can be used to demonstrate granules in paraffin sections (40). Tumor cells contain a small amount of cytoplasm with sparse nuclear chromatin. Neoplastic cells containing pink to red or red-purple cytoplasmic granules are usually present in Romanowsky-stained peripheral blood smears, but granules are not visible in hematoxylin and eosin stained fixed tissue sections. Ultrastructurally, the granules are readily visible in some, but not all, neoplastic cells.

In F344 rats, the disease appears to originate in the marginal zone of the spleen and rapidly spreads to other organs (21). Liver involvement ranges from a small number of isolated leukemic cells in the sinusoids in early cases to large accumulations of neoplastic cells resembling lymphoblastic lymphoma in more advanced cases. Leukemia is a common feature. How to stage or grade LGL lymphoma is described in the Discussion section.

TUMORS OF THE MONONUCLEAR PHAGOCYTE SYSTEM

Histiocytic Sarcoma (Figures 26-28)

Diffuse involvement of the liver often occurs in histiocytic sarcoma, and skin, subcutaneous tissue, and peritoneum are frequently involved. Multiple organs including the kidneys, lymph nodes, bone marrow, and ovaries may also be involved. Cells are large and monomorphic with dark, basophilic nuclei and prominent cosinophilic cytoplasm. Neoplastic cells are immunoreactive for lysozyme, vimentin, and ED-1 (7). The disease tends to be more fibrous in some tissues and palisading of cells is seen. Neoplastic cells tend to be non-cohesive in the liver and cohesive in the subcutaneous tissue. Giant cells may be prominent, and metastasis to the lungs is common. The disease may result in myeloid hyperplasia of the spleen and hyaline droplets containing lysozyme in renal proximal tubules (17).

MYELOGENOUS LEUKEMIA

Granulocytic Leukemia (Figures 29-31)

Granulocytic leukemia involves the liver, spleen, lymph nodes, and bone marrow. Kidney involvement appears to be common in the rat (18). Neoplastic cells usually represent a single immature or mature developmental stage, but in some cases cells in various developmental stages may be seen. When immature cells predominate, cells are large and blastic and segmented or lobed nuclei are scarce. Neoplastic cells are immunoreactive for lysozyme (41). Granulocytic leukemia is a rare spontaneous disease in rats (18) and must be distinguished from myeloid metaplasia.

Erythroid Leukemia (Figures 32-36)

Erythroid leukemia (erythroleukemia) is a rare disease in the rat. The disease is characterized by an excessive proliferation of erythroblastic cells, which may also contain cells of the granulocytic series. At necropsy, severe hepatosplenomegaly and enlargement of the lymph nodes throughout the body are observed. Bone marrow, thymus, spleen, liver, kidneys, and lymph nodes contain cells of the erythrocytic series, many of which are erythroblastic in appearance. Blood smear preparations contain numerous abnormal cells of the erythrocytic and granulocytic cell series. Ultrastructurally, neoplastic erythroblastic cells have round to oval nuclei with thick, coarse chromatin.

Basophilic Leukemia

Basophilic leukemia has not been reported to occur spontaneously in rats, but has been induced in Wistar rats (10, 22).

MAST CELL TUMOR (Figure 37)

A single case of mast cell neoplasia has been reported in the rat (20). Neoplastic mast cells are slightly larger than normal and the cytoplasm has a faint dust-like appearance when stained with H&E. Giemsa and toluidine blue stains reveal metachromatic granules in the cytoplasm.

THYMOMA (Figures 38-40)

The term thymoma is used to classify a lesion characterized by a neoplastic epithelial component with or without neoplastic lymphocytes (19). The epithelial component, positive for keratin, appears to be derived from the epithelial cells in Hassall’s corpuscles or thymic reticular tissue. Thymic epithelium may be either a majority of the tumor mass or a minor component; the neoplasm may assume either a carcinoma or a sarcoma appearance. Thymomas rarely metastasize.
<table>
<thead>
<tr>
<th>Type of Neoplasm</th>
<th>Cell Size</th>
<th>Cytoplasmic Features</th>
<th>Nuclear Features</th>
<th>Other Features</th>
<th>Anatomic Features</th>
<th>Antigens Detected by Immunocytochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCC Lymphoma</td>
<td>Intermediate to large (8-16 µm)</td>
<td>Scant to moderate</td>
<td>Cleaved and non-cleaved; prominent nucleoli</td>
<td>Cohesive; low mitotic rate</td>
<td>Early lesions are confined to spleen and mesenteric lymph nodes</td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td>Lymphoblastic Lymphoma</td>
<td>Small to large (7-12 µm)</td>
<td>Scant</td>
<td>Round to oval; prominent nucleoli</td>
<td>Uniform; noncohesive; intermediate mitotic rate</td>
<td>Diffuse organ involvement; secondary leukemia</td>
<td>Immunoglobulins or T-cell antigens</td>
</tr>
<tr>
<td>Immunoblastic Lymphoma</td>
<td>Large (10-18 µm)</td>
<td>Moderate to abundant; amphophilic</td>
<td>Vesicular; often eccentric; large and prominent nucleoli</td>
<td>Usually noncohesive; intermediate to high mitotic rate</td>
<td>Invasive sarcomatous pattern</td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td>LGL Lymphoma</td>
<td>Small (6-10 µm)</td>
<td>Scant; granules visible with EM and in blood smears or imprints of spleen</td>
<td>Round; often eccentric; small nucleoli, reniform</td>
<td>Usually noncohesive; low mitotic rate</td>
<td>Early lesions are confined to spleen and liver; secondary leukemia</td>
<td>OX-8, Granule Antigens</td>
</tr>
<tr>
<td>Granulocytic Leukemia</td>
<td>Variable</td>
<td>Granules</td>
<td>Lobed or ring nuclei</td>
<td>Mature or blastic</td>
<td>Secondary leukemia</td>
<td>Lysozyme</td>
</tr>
<tr>
<td>Histiocytic Sarcoma</td>
<td>Intermediate to large (8-16 µm)</td>
<td>Moderate to abundant</td>
<td>Large and irregular</td>
<td>Cohesive or noncohesive; multinucleated cells</td>
<td>Subcutaneous involvement; multinucleated giant cells; fibrosis</td>
<td>Lysozyme; Vimentin; ED-1</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Lymphoid and epithelial cells</td>
<td>May assume glandular pattern, sarcoma, carcinoma</td>
<td>Keratin</td>
</tr>
</tbody>
</table>
DISCUSSION

Terminology used to report the incidence of hematopoietic neoplasms in rats is quite varied (2, 16, 27, 41). It is important in toxicity and carcinogenicity studies to distinguish lymphoid cell neoplasms from non-lymphoid cell neoplasms when diagnosing proliferative lesions of the hematopoietic system.

The overall incidence of hematopoietic neoplasms, exclusive of LGL lymphoma, is generally much lower in rats than in mice. The most common hematopoietic lymphoid neoplasm in Fischer 344 and Wistar/Furth rats is LGL lymphoma, the incidence of which may be greater than 50% in animals two years or older (35, 42). This highly lethal tumor can affect group survivability and therefore can potentially impair the reliability of tumor bioassays (21, 35). Other lymphomas, including lymphoblastic and follicular center cell types, are rare in the F344 rat. The incidence of LGL lymphoma in other strains of rats is much lower. Frith (11) reported an incidence of 0.50% in both male and female Sprague-Dawley rats.

LGL lymphoma can be staged or graded depending upon its severity (9). Stage 1: The spleen is normal to slightly enlarged in size with small numbers of neoplastic LGL lymphocytes in the red pulp; no or very few neoplastic cells are found in the liver sinusoids and no identifiable neoplastic cells are found in other organs. Stage 2: The spleen is moderately enlarged with moderate to large numbers of LGL lymphocytes in the red pulp; architectural features including lymphoid follicles and periarial lymphoid sheaths remain intact; minimal to moderate involvement of the liver; aggregates/masses of neoplastic cells generally limited to the blood vessels of the spleen and liver, but neoplastic cells may be evident in other organs. Stage 3: The disease is advanced with multiple organ involvement; spleen usually markedly enlarged with effacement of the normal architectural features by accumulated neoplastic cells; liver moderately to markedly enlarged and nodular; hepatic parenchyma shows variable degenerative changes associated with the accumulation of neoplastic cells; accumulations of neoplastic cells in other organs, including lungs, lymph nodes, kidneys, brain, and adrenal glands.

Follicular center cell (FCC) lymphomas are not well characterized in rats but are occasionally reported (11). They have been referred to in the mouse as reticulum cell sarcoma, type B (8) and pleomorphic or mixed cell lymphoma (4, 5, 15), and in the rat as reticulum cell sarcoma. More recent research involving immunology in mice and humans indicates the entity is derived from B lymphocytes or follicular center cells (14, 25, 26).

Therefore, the term FCC lymphoma is the preferred term for this disease.

The most common non-lymphoid hematopoietic neoplasm in the rat is the histiocytic sarcoma. The incidence was reported to be approximately 1.0% in both male and female Sprague-Dawley rats (11). Histiocytic sarcoma has been referred to as malignant fibrous histiocytoma (30, 39) and histiocytic sarcoma (1, 3, 6, 11, 29) in the rat, and as reticulum cell sarcoma, type A (8), histiocytic lymphoma (12), and histiocytic sarcoma (4, 5, 14) in the mouse. The preferred term is histiocytic sarcoma.

Erythroid leukemia appears to be a rare entity in both the rat and mouse. It has been described in rats after radiation and trimethylbenz[a]anthracene treatment (36), while the majority of reported cases in the mouse are associated with experimental inoculation of either the Friend leukemia virus (FLV) or the Rauscher virus. Rare spontaneous cases of erythroid leukemia have been reported in the female SIC:SD rat (24) and in the mouse (13).

Murray et al. (23) described the incidence, morphology, and ultrastructure of spontaneous thymomas in an inbred Wistar/Neuherberg strain of rat. Spontaneous thymomas were observed with an incidence of 97% and 36% in female and male rats, respectively. The thymomas often cause dyspnea and were occasionally the direct cause of death. The neoplasms resembled human thymomas, having a variable cell composition ranging from lymphocytic to epithelial.

In summary, the rat is an extremely valuable animal model for use in biomedical and toxicological research. The specific type of hematopoietic neoplasm may be important, and lymphoid cell neoplasms should be separated from non-lymphoid cell neoplasms in determining the toxicity and carcinogenicity of test substances.

RECOMMENDED NOMENCLATURE AND DIAGNOSTIC CRITERIA

NON-NEOPLASTIC LESIONS

Spleen

Hyperplasia, Red Pulp (Hematopoiesis)

1. Increase may occur in red cells (erythropoiesis), white cells (granulopoiesis), or megakaryocytes (megakaryocytosis) in response to inflammatory, neoplastic, or other insults
2. May increase in response to stimuli (reactive hematopoiesis) such as anemia, immune stimulation, and thrombocytopenia or to certain neoplasms
Hyperplasia, White Pulp
1. Increase may occur in the T-cell zone, periarteriolar lymphoid sheath (PALS), follicular B-zone, and/or marginal zone
2. T-cell hyperplasia may be seen in early metastatic thymic T-cell lymphomas and other lymphomas or leukemias
3. Hyperplasia of the follicular B-zone (follicular hyperplasia) of the white pulp occurs in acute and chronic immune responses to antigens and/or administration of certain chemicals

Focal Lymphoid/Histiocytic Hyperplasia
1. Consists of a sheet of mature lymphocytes containing scattered clusters of pale staining macrophages
2. Focal expansive lesion may be up to a centimeter in diameter

Plasmacytosis
1. Often accompanies myeloid hyperplasia or inflammatory or proliferative lesions in other organs
2. Mature plasma cells have a characteristic purple to intensely eosinophilic cytoplasm, eccentrically located nuclei, and cartwheel-patterned nuclear chromatin
3. Plasma cells and their precursors are readily distinguishable after staining for immunoglobulins

LYMPH NODE

Hyperplasia
1. May occur in the cortex or medulla
2. Hyperplasia of the paraconter may include lymphocytes, large granular lymphocytes, and interdigitating reticular cells
3. In normal response to antigens, follicles develop hyperplastic germinal centers containing immature B-cells

Plasmacytosis
1. Common finding in mandibular lymph nodes
2. Plasma cells are located predominantly in the medullary cords and may contain Russell’s bodies
3. Mature plasma cells have a characteristic purple to intensely eosinophilic cytoplasm, eccentrically located nuclei, and cartwheel-patterned nuclear chromatin

Sinus Histiocytosis
1. Characterized by the presence of reactive histiocytes in the sinuses
2. Cytoplasm of the histiocytes has a distinct eosinophilic appearance and may contain hemosiderin and other phagocytized materials

Mastocytosis
1. Increase above normal number of mast cells

THYMUS

Hyperplasia
1. Hyperplasia may involve lymphoid or epithelial elements which may occur independently or in conjunction with each other
2. Lymphoid hyperplasia involves either the cortex or the medulla
3. Lymphoid hyperplasia is characterized by areas of dark staining lymphocytes; usually occurs in atrophic thymuses

BONE MARROW

Hyperplasia
1. Increases in both erythrocytic and granulocytic cell lines
2. Granulocytic component usually predominates

Mastocytosis
1. Increase in number of normal mast cells in the bone marrow
2. Cause is usually unknown

NEOPLASTIC LESIONS

LYMPHOMAS

Follicular Center Cell (FCC) Lymphoma
1. May range in size from small to large or be a mixture of cell sizes
2. Cells are cohesive and the cytoplasm is abundant in larger cells
3. Cleaved or non-cleaved nuclei; low mitotic index
4. Larger cells tend to have vesicular nuclei with prominent nucleoli
5. Tumor cells contain immunoglobulins which can be demonstrated by immunocytochemistry
6. Spleen, liver, and lymph nodes are commonly involved

Plasma Cell Lymphoma
1. Small to large non-cohesive cells with abundant amphophilic cytoplasm
2. Round to oval nuclei with irregularly margined, condensed chromatin
3. Variable mitotic activity
**Immunoblastic Lymphoma**
1. Large non-cohesive cells with conspicuous amphophilic cytoplasm
2. Large vesicular nuclei with multiple conspicuous nucleoli
3. Plasmaeyoid features may be prominent
4. Mitotic index is intermediate to high
5. Spleen, liver, and lymph nodes commonly involved; very invasive

**Lymphoblastic (Lymphocytic) Lymphoma**
1. Cells are non-cohesive and vary in size, but tend to have a uniform appearance
2. Scant cytoplasm and round nuclei with multiple prominent nucleoli
3. Intermediate to high mitotic index
4. Spleen, liver, lymph nodes, thymus, bone marrow, and kidneys commonly involved; leukemia often occurs

**Large Granular Lymphocyte (LGL) Lymphoma (Leukemia)**
1. Cells are non-cohesive, small, and pleomorphic with scant cytoplasm
2. Nuclei are irregular, round to reniform, and often eccentric with sparse chromatin and small nucleoli; mitotic rate is low
3. Tumor cells are OX-8 immunoreactive and antibodies to granule antigens such as serine esterase can be used to demonstrate granules in paraffin sections; granules are pink to red or red-purple in Romanovski-stained peripheral blood smears
4. The disease originates in the marginal zone of the spleen and rapidly spreads to other organs; leukemia is a common feature
5. Liver involvement ranges from a small number of isolated leukemic cells in the sinusoids in early cases to large accumulations of neoplastic cells resembling lymphoblastic lymphoma in more advanced cases
6. Can be staged or graded (Stage 1, 2, or 3) depending upon extent of disease

**MONONUCLEAR PHAGOCYTE SYSTEM**

**Histiocytic Sarcoma**
1. Cells are large and monomorphic with large, dark, irregular, basophilic nuclei and abundant eosinophilic cytoplasm which is positive for lysozyme
2. Skin, subcutaneous tissue, and peritoneum are frequently involved; the kidneys, lymph nodes, bone marrow, and ovaries may also be involved
3. Diffuse involvement of the liver often occurs and giant cells may be prominent; metastasis to the lungs is common
4. Neoplastic cells tend to be non-cohesive in the liver and cohesive in the subcutaneous tissue
5. Neoplastic cells are immunoreactive for lysozyme, vimentin, and ED-1
6. May result in myeloid hyperplasia of the spleen and hyaline droplets containing lysozyme in the renal proximal tubules

**MYELOGENOUS LEUKEMIA**

**Granulocytic Leukemia**
1. Cells in various developmental stages
2. When immature cells predominate, cells may be large and blastic; segmented or lobed nuclei may be scarce
3. Disease usually is leukemic and involves the liver, spleen, lymph nodes, and bone marrow
4. Kidney involvement appears to be common
5. Neoplastic cells are immunoreactive for lysozyme

**Erythroid Leukemia**
1. Characterized by an excessive proliferation of erythrogenic cells; may also contain cells of the granulocytic series
2. Cells have dark cytoplasm and round to oval nuclei with thick and coarse chromatin and large nucleoli
3. Circulating abnormal cells of erythrocytic and granulocytic cell series; bone marrow, thymus, spleen, liver, kidneys, and lymph nodes contain cells of the erythrocytic series, many of which are erythroblastic in appearance
4. At necropsy, severe hepatosplenomegaly and enlargement of the lymph nodes throughout the body may be observed

**Basophilic Leukemia**
1. Extremely rare spontaneous disease in rats

**MAST CELL TUMOR**
1. Neoplastic mast cells are slightly larger than normal and the cytoplasm has a faint, dust-like, basophilic appearance when stained with H&E
2. Giemsa and toluidine blue stains reveal metachromatic granules in the cytoplasm of the neoplastic mast cells

**THYMOtMA**
1. Neoplastic epithelial component with or without neoplastic lymphocytes
2. Epithelial component is positive for keratin cytofilaments; may be a majority of the tumor
mass or a minor component
3. May assume either a carcinoma or a sarcoma appearance
4. Rarely metastasizes

REFERENCES


Fig. 1 – Hyperplasia (erythropoiesis) of the red pulp, spleen (H&E).

Fig. 2 – Hyperplasia (granulopoiesis) of the red pulp, spleen. Note concomitant increase in megakaryocytes (arrow)(H&E).

Fig. 3 – Hyperplasia (granulopoiesis) of the red pulp, spleen. Double immunostaining for lysozyme in granulocytes (brown) and IgG in plasma cells (black). (Avidin-Biotin Complex technique).

Fig. 4 – Hyperplasia of the white pulp, spleen; rat injected with E. coli (H&E).
Fig. 5 – Focal lymphoid/histiocytic hyperplasia, spleen (H&E).

Fig. 6 – Higher magnification of Fig. 5 showing pale staining macrophages (H&E).

Fig. 7 – Follicular hyperplasia, lymph node (H&E).

Fig. 8 – Plasma cell hyperplasia, submandibular lymph node. Top: H&E. Bottom: higher magnification.
**Fig. 9** – Plasmacytosis, lymph node. Plasma cells are immunopositive for IgG (Avidin-Biotin Complex technique).

**Fig. 10** – Sinus histiocytosis, lymph node (H&E).

**Fig. 11** – Focal areas of lymphoid hyperplasia, atrophic thymus of an old rat (H&E).

**Fig. 12** – Mixture of lymphoid and epithelial hyperplasia, atrophic thymus of an old rat (H&E).
Fig. 13 – Follicular center cell (FCC) lymphoma. Top: mesenteric lymph node (H&E). Bottom: liver (H&E).

Fig. 14 – Plasma cell lymphoma, lymph node (H&E).

Fig. 15 – Immunoblastic lymphoma. Top: H&E stain. Bottom: cells are immunopositive for IgG (Avidin-Biotin Complex technique).

Fig. 16 – Lymphoblastic (lymphocytic) lymphoma, lymph node (H&E).
Fig. 17 – Higher magnification of Fig. 16 (H&E).

Fig. 18 – Gross photograph of a Fischer 344 rat with LGL lymphoma (leukemia). Note enlarged spleen.

Fig. 19 – Spleen cell prep from F344 rat with LGL lymphoma showing LGL leukemia cells and normal lymphocytes (Giemsa).

Fig. 20 – Early (Stage 1) LGL lymphoma (leukemia), liver (H&E).
Fig. 21 – More advanced (Stage 2) LGL lymphoma (leukemia), liver (H&E).

Fig. 22 – LGL lymphoma (leukemia), spleen (H&E).

Fig. 23 – LGL lymphoma (leukemia); cells are OX-8 immunopositive (Avidin-Biotin Complex technique).

Fig. 24 – Electron micrograph of LGL lymphoma demonstrating large granules in the cytoplasm (uranyl acetate - lead citrate).
Fig. 25 – Electron micrograph of individual neoplastic large granular lymphocyte (uranyl acetate - lead citrate).

Fig. 26 – Histiocytic sarcoma, liver (H&E).

Fig. 27 – Histiocytic sarcoma, skin/subcutaneous tissue. Top: note giant cells (H&E). Bottom: neoplastic histiocytes are immunopositive for lysozyme (Avidin-Biotin Complex technique).

Fig. 28 – Histiocytic sarcoma metastasis to the lungs adjacent to a bronchiale (H&E).
Fig. 29 – Granulocytic leukemia, liver (H&E).

Fig. 30 – Granulocytic leukemia, kidney (H&E).

Fig. 31 – Granulocytic leukemia. Neoplastic granulocytes are immunopositive for lysozyme (Avidin-Biotin Complex technique).

Fig. 32 – Smear of peripheral blood of a rat with erythroid leukemia. Note neoplastic erythrocyte (A) and neoplastic granulocyte (B) (May-Giemsa stain). Reprinted with permission of the Toxicologic Pathology (24).
Fig. 33 – Erythroid leukemia, liver. Numerous neoplastic cells have infiltrated the sinusoids, and hepatocytes are compressed and atrophic (H&E). Reprinted with permission of Toxicologic Pathology (24).

Fig. 34 – Erythroid leukemia, spleen. Top: cells immunopositive for hemoglobin (streptavidin-biotin peroxidase & hematoxylin). Bottom: positive peroxidase reaction in the cytoplasm (hematoxylin). Reprinted with permission of Toxicologic Pathology (24).

Fig. 35 – Electron micrograph of a neoplastic erythroblastic cell (uranyl acetate - lead citrate). Reprinted with permission of Toxicologic Pathology (24).

Fig. 36 – Electron micrograph of a neoplastic granulocytic cell with a large nucleus and prominent nucleoli (uranyl acetate - lead citrate). Reprinted with permission of Toxicologic Pathology (24).
Fig. 37 – Mast cell tumor, subcutaneous tissue. Top: H&E. Bottom: toluidine blue. Photos courtesy of Dr. L. Lingered, Pfizer, Ambérieu, France.

Fig. 38 – Thymoma: mixture of lymphoid and epithelial components (H&E).

Fig. 39 – Thymoma: epithelial component is immunopositive for keratin (Avidin-Biotin Complex technique).

Fig. 40 – Electron micrograph of thymoma showing lymphocytes and epithelial cells (uranyl acetate-lead citrate). Reprinted with permission of the Journal of the National Cancer Institute (23).