ANIMAL MODEL OF HUMAN DISEASE

Hodgkin's Disease

SJL/J Murine Lymphoma

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Biologic and Pathologic Features

Inbred strain SJL/J mice (Jackson Laboratories, Bar Harbor, Maine) exhibit a high incidence and early onset of a spontaneous lymphoma, which has been proposed as a possible model of human Hodgkin's disease. Murphy[1] initially reported a 91% incidence of tumors at a mean age of 13.3 months, but most subsequent series[2-6] have recorded a somewhat lower incidence, generally ranging from 40% to 85% in females and from 15% to 70% in males. Tumors have been observed with increasing frequency after about 5 months of age.

Serial morphologic studies have established that a phase of plasma cell proliferation in lymphoid tissue precedes the onset of overt neoplasia. This may be the basis of the IgG paraproteinemia and hypergammaglobulinemia that often accompany the development of lymphoma. Neoplastic involvement is usually first noted in the mesenteric lymph node complex. Simultaneous neoplastic enlargement of Peyer's patches may be observed. Splenomegaly is frequent. Various other groups of lymph nodes may be involved later (Figure 1). Visceral infiltration, particularly affecting the liver, lungs, and thymus, may also be noted in advanced disease. Bone marrow infiltration does not occur, and no leukemic phase develops.

Histopathologically the SJL/J lymphoma most frequently resembles mixed-cellularity Hodgkin's disease; however, as in human Hodgkin's disease, the cellular composition of the neoplastic infiltrates varies considerably between different tumors. The typical microscopic appearance is of numerous "neoplastic reticulum cells," occasional Reed-Sternberg-like tumor giant cells (Figure 2), and a pleomorphic cellular background that may include lymphocytes, plasma cells, eosinophils and neutrophils. Lacunar cell variants are often observed; and, less frequently, a granulomalike pattern or epithelioid cell-like pattern of tumor cells may be noted. The cellular background may range from a predominance of lymphocytes or plasma cells to lymphocyte depletion. Fibrosis is occasionally noted but is usually minimal. Reticulin staining reveals a mild increase in reticulin fibrils within an involved lymph node, some of which appear to be associated with neoplastic cells.

The spontaneous SJL/J lymphoma grows relatively slowly, and the general condition of tumor-bearing animals does not deteriorate until late in the course of the disease. A mean survival time of 14 weeks from the onset of detectable tumor involvement has been recorded.[2]

Unlike other spontaneous malignancies of inbred mice, transplantability is not an invariable feature of the SJL/J murine lymphoma, because only about 30–55% of primary neoplasms grow in syngeneic recipients.[2,3,7] Following subcutaneous or intraperi-

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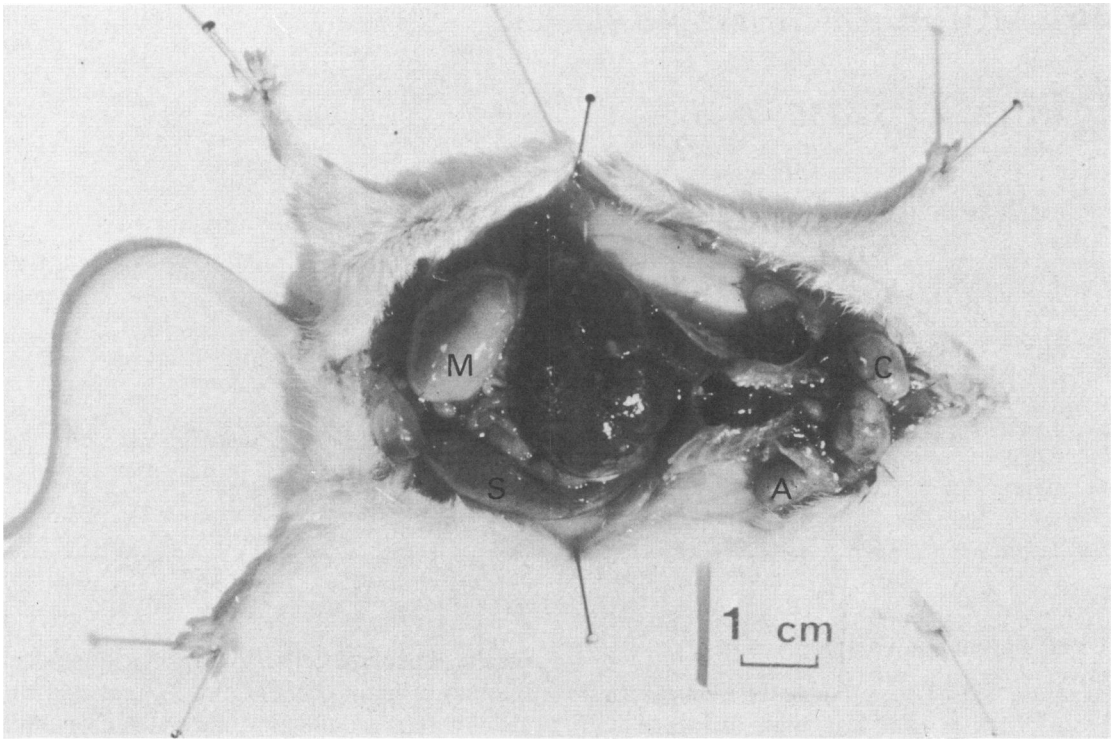

Figure 1 – Generalized involvement of lymph nodes and viscera in advanced spontaneous SJL/J murine lymphoma. Note enlargement of cervical (*C*), axillary (*A*), and mesenteric (*M*) lymph nodes, splenomegaly (*S*), and tumor infiltrates in the liver.

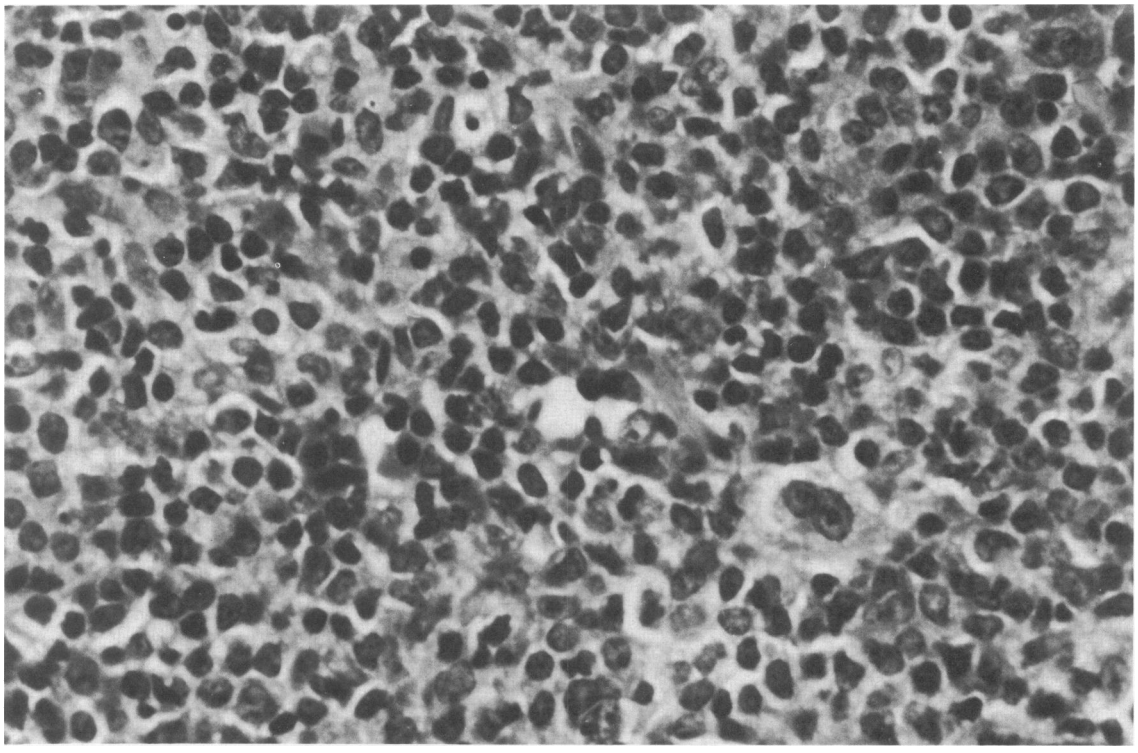

Figure 2 – Typical Reed-Sternberg-like tumor giant cell in mesenteric lymph node involved by SJL/J murine lymphoma. Note the symmetric vesicular nuclei and prominent nucleoli that stained with eosin. Cellular background includes a predominance of lymphocytes and a few eosinophils. (H&E, × 440)

Table 1—Comparison of SJL/J Murine Lymphoma With Human Hodgkin's Disease

A. Similarities
1. Histopathologic features
2. Onset in young to middle adult life
3. Gradual progressive involvement of lymphoid tissues and viscera with long survival
4. Surface markers on tumor cells (Fc and complement receptors; Ia antigens)
5. Immunobiologic features
B. Differences
1. Host characteristics (inbreeding)
2. High immunogenicity*
3. Probable viral etiology*
4. Possible origin from B cells*

* Potential differences only because these issues are currently unresolved for human Hodgkin's disease.

toneal inoculation of pieces of tumor tissue or tumor cell suspensions, local growth is generally not seen, but the tumor disseminates and involves lymph nodes, spleen, and liver. Histopathologically, the transplanted tumor usually resembles the primary lesion in its cellular heterogeneity, at least in early transplant generations. However, during subsequent transplant generations there is usually a progressive reduction in the diversity of cell types, and the neoplasm eventually grows as a reticulum cell sarcoma. In most animals, transplanted tumors grow progressively and typically prove fatal in 3–5 weeks, although survival times may be considerably shorter in later transplant generations. A proportion of mice have spontaneous and apparently complete regression of tumors.[8] Reinjection and adoptive transfer experiments have demonstrated that the neoplasm is highly immunogenic and that different *in vivo* transplantable lines of the SJL/J lymphoma bear different transplantation antigens. The tumor is extremely difficult to maintain in *in vitro* culture, although some workers have reported successful establishment of cell lines.[9,10]

Information about the etiopathogenesis of the SJL/J murine lymphoma is currently inadequate. However, it appears probable that the neoplasm has a viral etiology, although ultrastructural evidence is inconclusive.[4,11] Attempts to induce the disease with cell-free filtrates of tumor tissue extracts have yielded confusing results.[5,12] The neoplastic cells may arise from transformed follicular B-lymphocytes but do not express surface markers typical of B cells[13]; some workers have proposed a possible origin from NK cells,[14] while others have postulated that the tumor cells are macrophage-derived.[15] The role of a preexisting immunodeficiency in the pathogenesis of the SJL/J lymphoma is not yet resolved; published studies to date have yielded conflicting information.[16–18] Recent studies have demonstrated tumor-induced suppression of host cell-mediated immune responses in tumor-bearing SJL/J mice, apparently mediated by a soluble plasma suppressor factor. This factor is probably produced by the tumor cells and is not related to an intact virus.[19,20]

Comparison With Human Disease

The diagnosis of Hodgkin's disease is essentially a histopathologic one based on the presence in involved tissues of characteristic Reed-Sternberg cells in an appropriate cellular and architectural environment. The extent of similarity of the microscopic features of the SJL/J murine lymphoma to those of Hodgkin's disease is therefore a crucial issue in validating the animal model. Morphologic studies have repeatedly affirmed the similarity of the two lymphomas, and the wide range of histopathologic types of human Hodgkin's disease is reproduced quite well in the SJL/J lymphoma. However, nodular sclerosis, which is the most common histopathologic type of human Hodgkin's disease, does not occur in the SJL/J lymphoma. Other similarities and differences are summarized in Table 1.

Usefulness of the Model

The SJL/J murine lymphoma provides a useful model for the study of the immunobiologic features of the tumor–host relationship in Hodgkin's disease. The use of a transplanted tumor system permits accurate definition of tumor onset; and a controlled, statistically valid longitudinal study of the changes in host immune responsiveness with respect to neoplastic progression and regression is feasible. The SJL/J lymphoma model is also useful for the study of mechanisms by which immunogenic tumor cells escape immunologic destruction and of the role of tumor-derived nonspecific immunosuppressive factors in neoplastic disease. Tumor-bearing SJL/J mice have also been used in experimental studies of therapeutic regimens for lymphomas.[21]

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