ANIMAL MODEL OF HUMAN DISEASE

Infantile X-Linked Agammaglobulinemia

Agammaglobulinemia in Horses

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Biologic Features

Agammaglobulinemia is a severe immune deficiency of horses observed in males of thoroughbred, standardbred, and quarter horse breeds. Clinical signs of pneumonia, enteritis, dermatitis, arthritis, and laminitis are noted at 2–6 months of age following catabolic elimination of maternally derived immunoglobulins. Death occurs from 2 to 18 months of age.[1-4]

Immunologic evaluation reveals an absence of B lymphocytes, undetectable concentrations of IgM and IgA, and very low concentrations of IgG and IgG(T). Affected horses produce no detectable antibodies following immunization. T-lymphocyte numbers are apparently normal, and adequate T-lymphocyte responses are obtained with the use of *in vivo* and *in vitro* functional assays, including reactivity to intradermal injection of phytohemagglutinin, lymphocyte binding of phytolectins, blastogenic response to phytolectin and antigen stimulation, and migration inhibition of leukocytes when in the presence of antigens to which the horse has been immunized.[1-3] Peripheral blood lymphocytes from one agammaglobulinemia horse tested contained normal amounts of adenosine deaminase activity.[2]

Histologic examination of lymphoid tissues reveals an absence of lymphoid follicles and plasma cells in lymph nodes and spleen (Figures 1 and 2). An additional lesion of diagnostic significance is found in the spleen and consists of an absence of the connective tissue stromal framework of lymphoid follicles. These structures are always observed in nondeficient horses and are readily apparent in horses where lymphoid depletion is the result of atrophy rather than a primary immunodeficiency disorder (Figure 3). The absence of this stromal tissue has only been observed in one other immunodeficiency disorder of horses, combined immunodeficiency, in which there is absence of both T and B lymphocytes.[5,6] The possibility exists that B lymphocytes exert an inductive influence on this stromal tissue.

The diagnosis of agammaglobulinemia is established on the basis of a normal lymphocyte count, an absence of B lymphocytes, and low or undetectable concentrations of IgM, IgA, IgG(T), and IgG in the presence of normal T-lymphocyte responses. These criteria differentiate agammaglobulinemic horses from those with combined immunodeficiency, selective IgM deficiency, or failure of passive immunoglobulin transfer from mare to foal.[4]

Comparison With Human Disease

Infantile X-linked agammaglobulinemia is one of six immunodeficiencies of man inherited as an X-linked trait.[7] Infantile X-linked agammaglobulinemic boys have repeated episodes of infections, beginning in the first few months of life.[8] While there is an absence or near absence of B lymphocytes, most patients have pre-B-lymphocytes, and a few are able to

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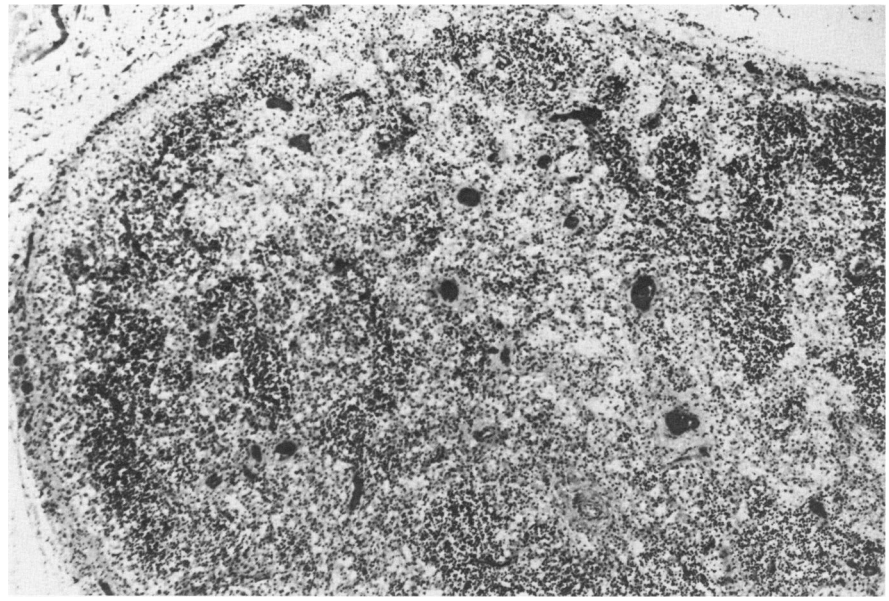

Figure 1—Lymph node from an agammaglobulinemic horse. Notice the absence of primary follicles and germinal centers.

produce small quantities of specific antibodies.[9-11] An inability of pre-B-cells to differentiate to B lymphocytes is a common finding. In some patients there are increased numbers and/or activity of suppressor T lymphocytes, which may contribute to the impaired transition of pre-B to B lymphocytes.[12,13]

Agammaglobulinemia in horses is the only spontaneously occurring animal model that closely resembles X-linked infantile agammaglobulinemia of boys.[14] All cases to date have occurred in males, suggesting but not proving an X-linked mode of inheritance in horses. The absence of B lymphocytes and plasma cells, the inability to produce antibodies following immunization, and the development of recurrent bacterial infections in early life are characteristics shared by affected horses and the majority of affected boys. It is not known whether affected horses have normal numbers of pre-B-cells. This question will be answered through study of future cases using monoclonal antibodies reactive with equine IgM for detection of cytoplasmic IgM in pre-B-cells.[15]

At least three important issues require solutions concerning the disease in man. These include 1) the biochemical basis of the disorder, including the role played by suppressor T lymphocytes in the failure of pre-B-cells to mature to functional B lymphocytes; 2) prospective identification of females carrying the trait; and 3) prenatal diagnosis of affected children.

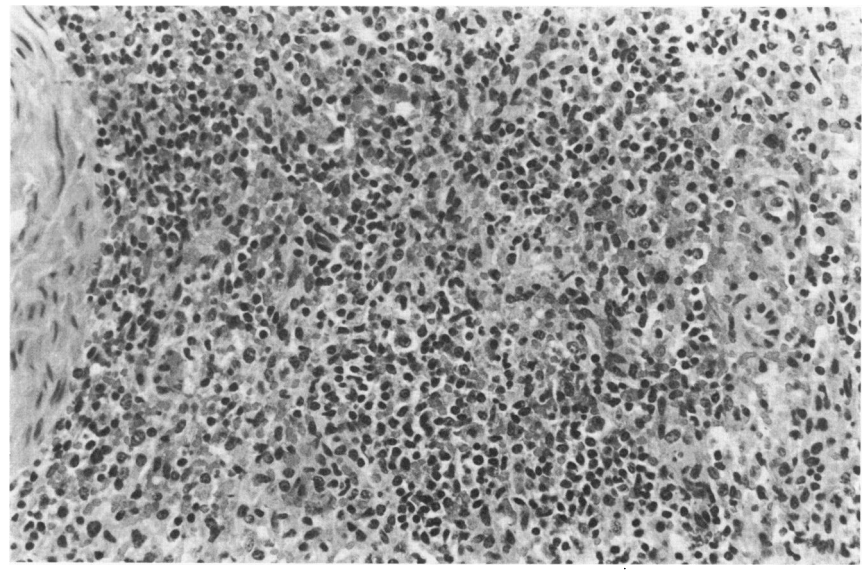

Figure 2—Spleen from an agammaglobulinemic horse. Notice the absence of lymphoid follicles and connective tissue stroma at sites where lymphoid follicles would normally be present.

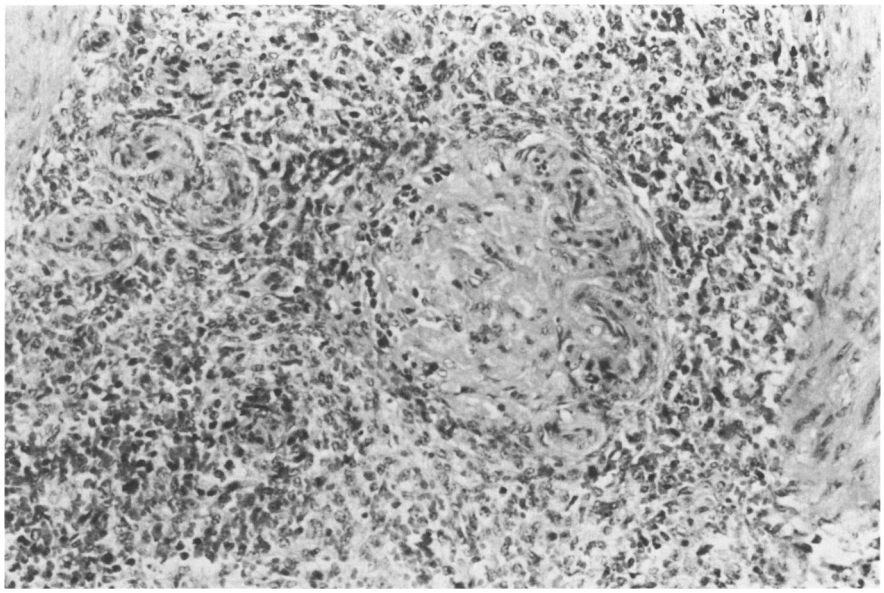

Figure 3—Spleen from a foal 10 days after lethal X-irradiation of 840 rads. In the absence of lymphocytes, the stromal support for lymphoid follicles remains. These structures are not observed in spleens from horses with agammaglobulinemia.

Usefulness of the Model

Since agammaglobulinemia in horses is the only animal model of infantile X-linked agammaglobulinemia, it may be useful in resolving the three issues stated above. With early diagnosis and appropriate care, affected animals can be maintained to at least 1½ years and probably to sexual maturity. Horses are of sufficient size to yield substantial numbers of lymphocytes for analysis on a daily basis. The availability of monoclonal antibodies reactive with equine immunoglobulins and T-lymphocyte subpopulations will facilitate characterization of B-lymphocyte differentiation and the roles played by T-lymphocyte subpopulations during those differentiation events.[15]

Availability

A survey of 2516 horses conducted at Washington State University led to the diagnosis of 4 cases of agammaglobulinemia.[4] Additional cases can be found by quantitating serum immunoglobulin concentrations in young horses, particularly males with a history of repeated infections.

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