Mouse Hepatitis Viral Infection, Adrenal, Mouse

Stephen W. Barthold

Synonyms. Hepatoencephalitis virus, murine hepatitis viral infection.

Gross Appearance

Mice that are ill or dying from mouse hepatitis virus (MHV) infection may have gross lesions in a number of organs, depending upon the infecting virus strain and a number of host factors. Livers may be diffusely pale, have random depressed white spots and petechiae, or be roughly nodular with depression of intervening parenchyma. Hepatitis may be accompanied by small amounts of peritoneal exudate. Mice infected with enterotropic strains may have dilated, fluid- and gas-filled intestines with thin, translucent walls. The spleen may be enlarged and the thymus reduced. The majority of infections in adult, immunocompetent mice are asymptomatic, with no gross lesions (Barthold 1987; Barthold et al. 1982, 1985; Biggers et al. 1964; Hierholzer et al. 1979; Piazza 1969). Depending upon infecting virus strain, athymic nude mice may develop wasting syndrome with neurological signs, hepatic lesions and splenomegaly (Hirano et al. 1975; Sebesteny and Hill 1974; Tamura et al. 1977). Nude mice infected with enterotropic strains of virus may have no overt disease or segmental thickening of the bowel wall, particularly the cecum and ascending colon, and mesenteric lymph node enlargement without hepatitis (Barthold et al. 1985).

Microscopic Appearance

Depending on virus and host factors, focal necrosis, leukocytic infiltration, and syncytium formation may be found in a variety of organs including liver, brain, spinal cord, olfactory mucosa, lung, lymphoid organs, pancreas, small intestine, cecum, and colon. Syncytia may arise from mesothelium, lymphoreticular cells, endothelium, glia, neurons, enterocytes, and parenchymal cells (Barthold 1987, 1988; Barthold and Smith 1987; Barthold et al. 1982, 1985, 1993; Biggers et al. 1964; Piazza 1969). Adrenal cortical or medullary cells may form syncytia in multisystemic viral infections (unpublished). Vacuolization of adrenal parenchyma, especially the zonae glomerulosa and fasciculate, and medullary edema and hyperemia have been reported in experimental MHV-3 infection (Piazza 1969).

Ultrastructure

Lytically infected cells develop a number of nonspecific degenerative changes. Viral particles are seen in dilated cisternae of endoplasmic reticulum and to a lesser extent within cytoplasm and cytoplasmic vesicles. Virions have a nonhomogeneous central nucleoid surrounded by a less dense peripheral ring and an envelope with spikes. The envelope is acquired by budding through internal cytoplasmic membranes. Virus leaves the cell by exocytosis or cytolysis. Tissue culture cells infected with MHV strain A59 develop round or oval reticular inclusions and tubular bodies measuring approximately 1–2 nm. Reticular inclusions are composed of 250–400 Å threads in a dense matrix of 35 Å granules. Tubular bodies are composed of tubular structures 160–250 Å in diameter which may be continuous with the cytoplasmic tubular system. Ribosomes are in the cytoplasmic matrix between tubules. Viral particles bud into the cisternae of the tubules (David-Ferreira and Manaker 1965). Tubular bodies also have been found in hepatocytes of MHV A59 infected mice and enterocytes of mice infected with MHV-Y (Barthold et al. 1982; Piazza 1969).

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Differential Diagnosis

When they can be found, syncytia are characteristic of MHV in many organs. Adrenal syncytia must be differentiated from clusters of hematopoietic elements or leukocytes. Adrenal lesions are likely to occur only in disseminated infections of susceptible hosts. Thus, evaluation of other more commonly affected tissues for MHV lesions is confirmatory.

Biologic Features

Natural History. The majority of natural MHV strains are only mildly pathogenic, and infections are likely to be subclinical. MHV infections may be manifest in a number of ways, depending on route of exposure, virus strain, dose, mouse strain, immunocompetency, age, and coinfection with other agents (Barthold 1987). Some strains are weakly pathogenic, even in athymic nude mice (Hirano et al. 1975), while others are highly virulent in adult mice (LePrevost et al. 1975). A common sign of infection is perturbed immune responsiveness of mice (Barthold 1987). MHV infections in immunocompetent mice are generally acute, with no persistence of the virus (Barthold and Smith 1987, 1990; Barthold et al. 1993). Misunderstanding about MHV persistence in mice has been perpetuated by observations of exacerbation of acute disease with immunosuppressive agents in subclinically infected mice (Barthold and Smith 1990; Piazza 1969). Exacerbation of disease can occur only in the early phase of infection, not after mice have recovered (Barthold and Smith 1990). Host immunity to MHV is virus strain specific, with immune mice susceptible to repeated subclinical reinfections with different strains of the virus (Barthold and Smith 1989; Homberger et al. 1992), thus suggesting persistence of virus when mice are immunosuppressed during active reinfection. Although mouse pups are most susceptible to disease, outbreaks of MHV in breeding populations are rapidly attenuated by maternal antibody, which protects young mice through their age-related susceptibility. Maternally derived immunity is short-lived, but once it has waned, mice are at an age when clinical signs are not apparent when they become infected (Barthold et al. 1988; Homberger et al. 1992). MHV is not likely to be vertically transmitted from dam to fetus (Barthold et al. 1988).

MHV strains, as coronaviruses of other species, have primary tropism for either respiratory or enteric mucosa. Respiratory MHV strains initially replicate in nasal mucosa, then readily disseminate in susceptible hosts to other organs. Enterotropic MHV strains tend to be much more selective in their tissue tropism, with infections restricted largely to the intestine. Thus, these two basic types of infection result in markedly different disease manifestations (Barthold 1987; Barthold and Smith 1987; Barthold et al. 1993). Enterotropic MHV strains tend to be highly contagious, causing severe disease in neonatal mice, with explosive outbreaks with high mortality when first introduced to a naive population. Neonates may die within 24–48 h of exposure (Barthold et al. 1982, 1993; Biggers et al. 1964; Hierholzer et al. 1979). Respiratory strains of MHV tend to be less contagious, but young mice are also most susceptible to disease manifestations, which include hepatitis and encephalitis (Barthold 1987; Barthold and Smith 1987). Neurotropism is an experimentally emphasized attribute of certain MHV strains and is usually a feature of the polytropic, respiratory types of virus, with development of encephalitis and demyelination upon intracerebral inoculation (Barthold 1987; Piazza 1969). Neurotropic strains of MHV can also infect brain directly via olfactory neural pathways or through viremia (Barthold 1988; Barthold and Smith 1987). Athymic nude mice and other immunologically compromised mice are prone to severe manifestations when infected with respiratory strains of MHV (Barthold et al. 1985; Hirano et al. 1975; Taguchi et al. 1979; Sebesteny and Hill 1974) but less so with enterotropic strains of MHV (Barthold et al. 1985).

Transplantable tumors, particularly leukemia lines, may become contaminated with MHV. The virus can be carried for many passages with no adverse effect but may break out following immunosuppression, chemotherapeutic regimens, or introduction into a susceptible host, resulting in acute disease or abnormal host tumor biology (Barthold 1987; Braunsteiner and Friend 1954).

Pathogenesis. MHV strains vary considerably in their virulence and relative organotropism but can be divided into respiratory and enteric biotypes (Barthold 1987). Respiratory strains of the

virus infect nasal epithelium (but not the lower respiratory epithelium), then disseminate in susceptible hosts to multiple organs. These viruses are pantropic, infecting and causing disease in many organs, of which the liver and brain are prominent because of their clinical effects. Brain infection can take place along olfactory neural pathways or via viremia. Lymphoid tissues are also a very common target, even in subclinically infected mice, resulting in immunological aberrations.

When respiratory viruses infect neonatal, athymic or other immunologically compromised strains of mice, their full disease manifestations become evident (Barthold and Smith 1987, 1990; Hirano et al. 1975). Immunocompetent mice vary in their susceptibility to MHV infection but recover from infection with no carrier state, although they can be reinfected with other strains of the virus (Barthold and Smith 1987, 1989). In contrast, enterotropic MHV strains are much more restrictive in their tissue tropism, targeting enterocytes and to a much lesser extent other tissues. Although mice of all ages are susceptible to infection, disease is highly age associated due to kinetics of intestinal epithelium. Infection of adult immunologically compromised mice, such as athymic nude mice, results in chronic infection, but clinical signs may be mild or absent (Barthold et al. 1982, 1985; Barthold and Smith 1990; Biggers et al. 1964; Hierholzer et al. 1979). Outcome of infection with MHV is highly dependent upon infecting virus strain, dose, route of inoculation, host age, genotype, and immune status (Barthold 1987).

Etiology. MHV is a coronavirus with numerous strains that vary widely in their biologic effects. MHV strains share extensive cross-reactive antigens, but host immunity to infection is virus strain specific (Barthold and Smith 1989; Homberger et al. 1992). To date there is no means of defining the biologic behavior or specific strain identity with genetic or antigenic means. This is irrelevant, as MHV is highly mutable and prone to recombination. Although the mouse is the natural host for MHV, rats can support experimental infections (Barthold and Smith 1989; Taguchi et al. 1979).

Frequency. MHV is very frequent in colonies of laboratory mice. The frequency of adrenal lesions in MHV-infected mice is low, as most infections are very mild without dissemination to organs such as the adrenal. They are most apt to be seen in immunologically compromised mice, such as nude mice, or in experimentally inoculated infant mice or mice infected with atypically virulent strains of MHV.

Comparison with Other Species

Coronaviruses are generally species specific, infect a number of host species, and have a wide spectrum of lesions, including peritonitis in cats, bronchitis in chickens, and enteritis in many species, especially in neonates. Like MHV, different strains of a particular species of coronavirus have either primary respiratory or enteric tropism. Human coronaviruses are generally associated with upper respiratory infections, and, as with mice, humans are subject to repeated infections with different strains of coronavirus (Barthold 1987).

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Adenovirus Infection, Adrenal, Mouse

Stephen W. Barthold

Gross Appearance

No lesion in the adrenal is visible to the naked eye in this infection.

Microscopic Appearance

Microscopic changes associated with this agent include inclusion body formation, necrosis, and inflammation in multiple organs (Heck et al. 1972). Adrenal changes occur primarily in all zones of cortical epithelium, but medullary cells and, less often, endothelium may be involved. Virus-induced inclusions are common and may be present in 80% of cortical epithelial cells in severe case (Figs. 517, 518). Inclusions vary in morphology depending upon stage of development. Inclusions appear first as slightly phloxinophilic single or paired ring forms or small spherules. Ring forms have sharply delineated, hematoxylinophilic outer and inner rims. Spherules are strongly phloxinophilic and vary in size up to the full capacity of the nucleus. Some spherules are surrounded by numerous tiny granules. Spherules later become dense and stain intensely with both pholxine and hematoxylin. Flower forms are very dense and are surrounded by radiating strands which divide the peripheral nucleus into septae. The cytoplasm of infected cells becomes eosinophilic and shrunken. Cellular disintegration intermixed with includion-bearing cells is usually seen. Leukocytic infiltration is frequent and most conspicuous in the late infection (Hoenig et al. 1974; Margolis et al. 1974).

Ultrastructure

Sequential changes in adrenal epithelium reflect a continuum of virus-host interaction, although cellular changes in a single specimen are always asynchronous with many stages occurring in different cells in the same area. The earliest change is an increase in the size and number of nucleoli, with the adjacent formation of round masses of finely punctate or fibrillar electron-dense material. These rounded masses detach and enlarge (E inclusion), some taking ring forms with electronlucent centers. E inclusions contain three components: (a) a finely fibrillar matrix of intermediate electron density (E_1); (b) a coarsely punctate component of high electron density, 150 Å granules (E_2); (c) highly electron-dense, finely granular material in irregular condensations throughout the matrix (E_3). Some E_3 material