K Virus Infection, Liver, Mouse

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Synonyms. None. However, K virus is also referred to as K-papovavirus.

Gross Appearance

Livers of infected animals, even those of suckling mice with fatal infection, are grossly normal.

Microscopic Features

Histopathologic changes due to K virus are most prominent in suckling mice, in which the virus produces a fatal infection. In older animals, K virus produces a clinically inapparent infection with minimal changes (Holt 1959; Greenlee 1979, 1981). However, even in newborn animals, histologic findings depend greatly on methods of tissue processing, and many features of the infection are obscured in conventional formalin-fixed, paraffin-embedded sections. Examination of routinely processed sections of livers from fatally infected suckling mice discloses a mild, diffuse infiltrate of polymorphonuclear leukocytes and occasional lymphocytes. Small numbers of cells lining hepatic sinusoids exhibit nuclear ballooning, but Cowdry type A intranuclear inclusions are rarely if ever observed. Many, but not all livers from fatally infected animals contain large numbers of membrane-bound, empty spaces. Inflammatory changes and nuclear ballooning are not present in livers of weanling or adult animals, even when viral infection can be demonstrated by immunofluorescence staining or virus assay (Greenlee 1981).

Identification of intranuclear inclusions within K virus-infected hepatic endothelial cells is greatly enhanced by fixation with Bouin's solution, 96% ethanol plus 1% glacial acetic acid, or *para*-toluenesulfonic acid. Diagnostic accuracy is also improved by use of paraffin or glycol methacrylate-embedded sections prepared at 2–3 μm thickness. Optimal detection of infected cells, however, requires staining of K virus capsid (V) antigen by immunoperoxidase techniques or study of adjacent sections by histologic and fluorescent antibody methods (Greenlee and Keeney 1982). Examination of infected livers by these methods reveals the presence of viral antigen in endothelial and Kupffer's cells, but not in hepatic parenchymal cells (Figs. 112, 113). Endothelial cells exhibit intense nuclear staining similar to that observed in productive infection by other members of the papovavirus group. Kupffer's cells contain cytoplasmic but not nuclear viral antigen, probably reflecting phagocytosis of circulating virions. Studies employing histologic and fluorescent antibody staining of adjacent sections reveal the vacuolar spaces sometimes present in K virus-infected livers to be lined with viral antigen, suggesting that these spaces are remnants of infected cells which have undergone lysis.

Ultrastructure

Limited ultrastructural studies of K virus infection have identified cytoplasmic virions within hepatic Kupffer's cells (Gleiser and Heck 1972; Jordan and Doughty 1969). Extensive ultrastructural examination of K virus-infected organs has not been reported.

Differential Diagnosis

Several other murine agents, including polyoma virus and murine cytomegalovirus, may involve livers and may produce intranuclear inclusions. None of these agents, however, is associated with an infection limited to endothelial cells. An important consideration in differential diagnosis is that hepatic involvement by K virus is almost invariably accompanied by significant interstitial pneumonia. This interstitial pneumonia, with ex-

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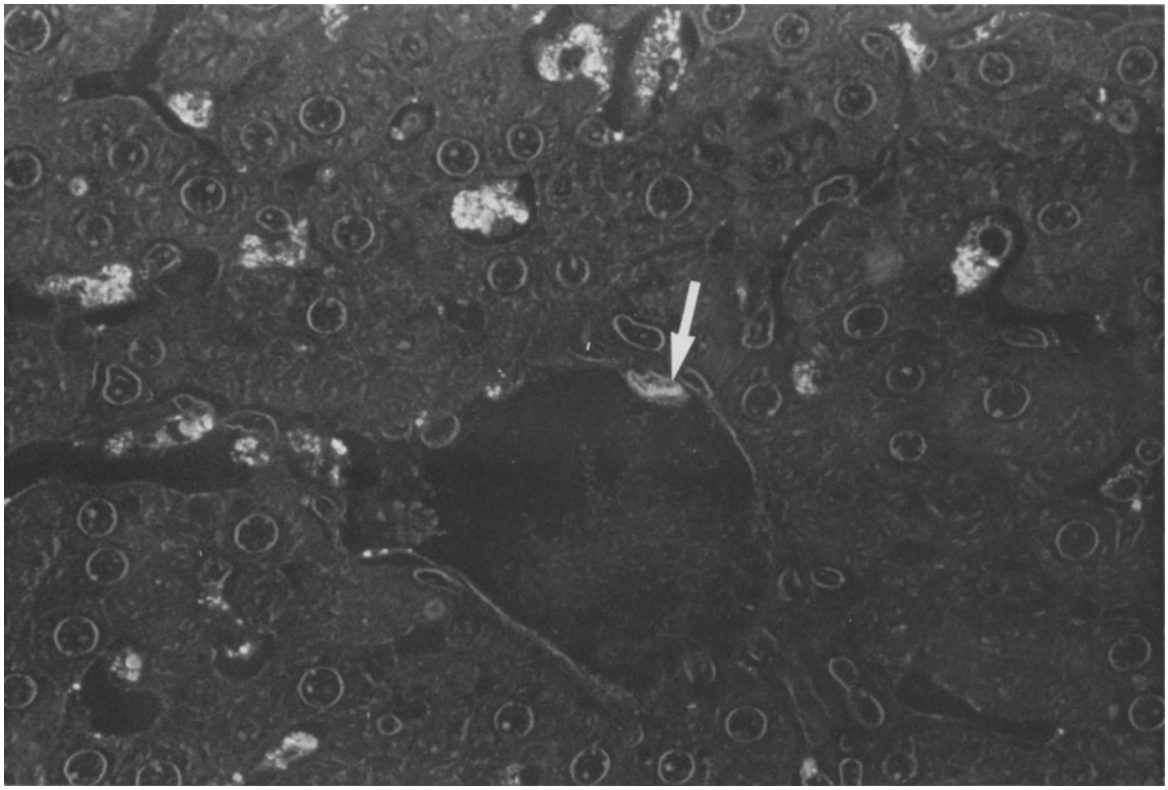

Fig. 112. Liver, mouse with lethal K virus infection. The section was fixed in 96% ethanol plus 1% glacial acetic acid, embedded in glycol methacrylate, sectioned at 2 μm thickness, stained for K virus capsid (V) antigen using indirect immunofluorescence methods, and examined using phase fluorescence microscopy. Nuclear fluorescence indicative of viral replication is present in the nucleus of an endothelial cell *(arrow)*. Numerous other cells contain cytoplasmic antigen without nuclear involvement, consistent with phagocytosis of circulating viral particles, × 300

tensive involvement of endothelial cells and sparing of bronchiolar and alveolar epithelia, is characteristic of K virus infection and is not duplicated by other murine viruses.

Biologic Features

K virus is a murine papovavirus which differs from the other known murine papovavirus, polyoma virus, in its genetic makeup and antigenic properties. K virus was initially identified in both wild and laboratory mice but is now rarely found in laboratory mouse colonies. The virus is believed to be transmitted in nature by the oral route, with initial replication of virus in capillaries of intestinal villi (Greenlee 1979). Epidemiologic studies indicate that infection with the virus usually occurs between 4 and 7 months of age. Two epidemiologic patterns of infection have been observed: antiviral antibody has been detected in the majority of animals within some colonies, but in others only a few animals have been found to have antibody (Parker et al. 1966; Tennant et al. 1966; Rowe et al. 1963). The major pathologic feature of K virus is its strong tropism for pulmonary and systemic vascular endothelial cells (Fischer and Kilham 1953; Kilham and Murphy 1953). In newborn mice, K virus causes an overwhelming respiratory infection in which intranuclear inclusions containing viral capsid antigen can be detected in endothelial cells of alveolar capillaries and larger pulmonary vessels. Smaller numbers of infected cells are present in capillary endothelia within virtually all other organs and tissues. Lungs, livers, spleens, and adrenals are most heavily involved. Fatally infected animals may also have viral antigen in occasional pulmonary alveolar epithelial cells. Immunohistologic examination of brains has suggested the presence of viral antigen in scattered central nervous system astrocytes, perineuronal satellite cells, and, rarely, oligodendrocytes, but definitive ultrastructural studies of K virus-infected brains have not

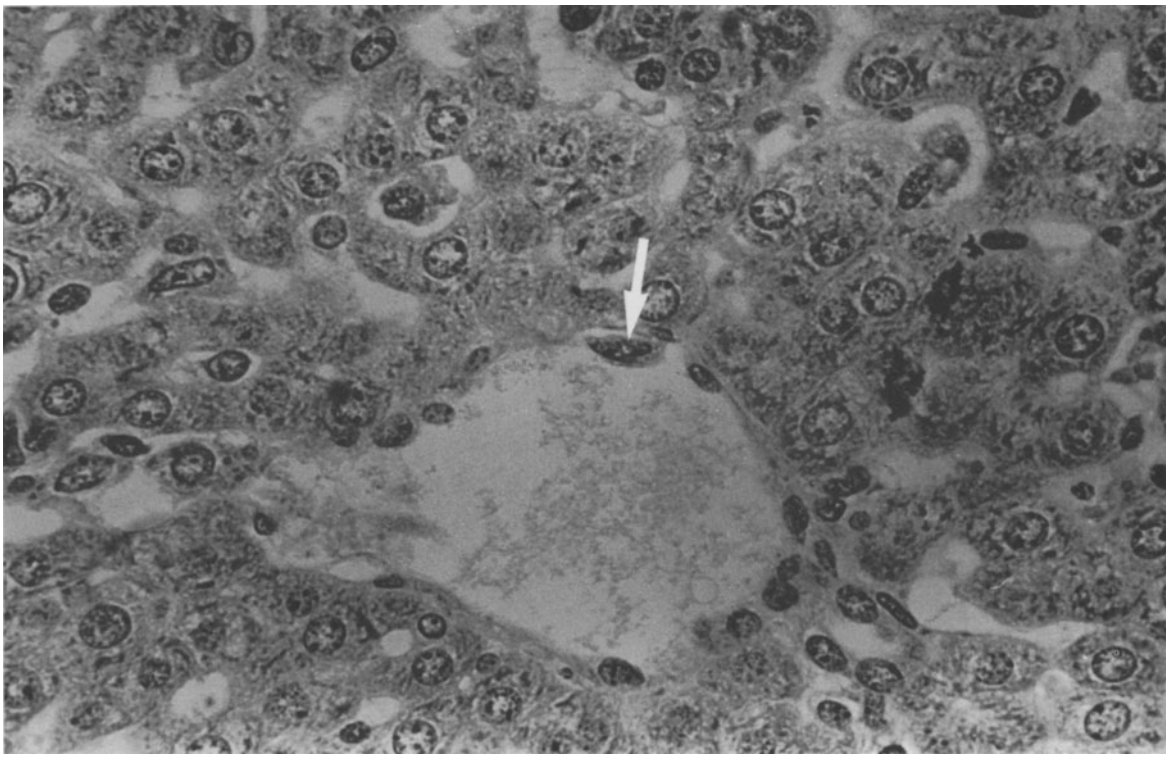

Fig. 113. Section adjacent to Fig. 112. The involved endothelial cell is indicated by the *arrow,* H and E, × 300

been reported (Greenlee 1983). Inoculation of older suckling, weanling, or adult animals results in a protracted, clinically silent infection with extent and distribution determined by the age and immunologic status of the animal at the time of inoculation (Greenlee 1981; Mokhtarian and Shah 1980, 1983). Infectious virus and viral antigen can be detected in organs of mice for up to 4–6 months after apparent clinical recovery. Immunosuppression of animals 8 months after inoculation results in the reappearance of viral antigen within most organs, but this reactivated infection is not accompanied by pathologic changes at a gross or microscopic level. Acute, primary infection in immunosuppressed adult animals, however, is similar in course and pathologic findings to acute infection in suckling animals.

Comparison with Other Species

K virus differs from other members of the papovavirus group in its ability to produce acutely fatal interstitial pneumonia in its natural host and in its strong tropism for vascular endothelial cells. A single case has been reported in which SV40 virus produced a fatal pneumonia in a laboratory primate, but the pulmonary infection in this animal was characterized by involvement of epithelial cells rather than endothelial cells (Sheffield et al. 1980). Murine polyoma virus has been shown to involve occasional vascular endothelial cells in brains of persistently infected nude mice (McCance et al. 1983); however, vascular involvement is not normally a feature of polyoma virus infection. DNA sequences homologous with those of human papovavirus JC have been found by *in situ* hybridization methods in cerebrovascular endothelial cells of one patient with progressive multifocal leukoencephalopathy (Dorries et al. 1979), but intranuclear inclusions or viral proteins have not been found in vascular endothelial cells or PML material by histologic or immunohistologic methods. Unlike other animal and human papovaviruses, K virus does not infect renal, ureteral, or bladder eipthelial cells, and renal infection by K virus is limited to endothelial cells of glomerular and parenchymal capillaries.

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Mouse Hepatitis Virus Infection, Liver, Mouse

Stephen W. Barthold

Synonyms. Hepatoencephalitis virus; murine hepatitis virus infection; mouse coronavirus infection.

Gross Appearance

Gross lesions can occur in liver, intestine, and lymphoreticular organs. Intestinal lesions are described in detail on p. 317. Affected livers have random small pale or hemorrhagic foci to multiple confluent foci with depression of the capsular surface. The liver may be diffusely pale and covered with fibrinous peritoneal exudate. Infant mice can be runted, jaundiced, or manifest neurologic signs including tremor, incoordination, or convulsions (Piazza 1969). During the acute phase of infection, involution of lymph nodes, spleen, and thymus can occur. Recovered mice develop mild spelenomegaly or lymphadenomegaly, particularly in cervical nodes. Athymic nude mice can become progressively cachectic (wasting disease). Their livers are contracted with rough, nodular surfaces (Ward et al. 1977), and splenomegaly can be pronounced (Ishida et al. 1978).

Microscopic Features

Depending on virus and host factors, foci of necrosis, leukocytic infiltration and syncytium formation may be encountered in many organs. Acute focal hepatocellular necrosis is accompanied by hemorrhage and mild mixed leukocyte infiltration. Lesions in susceptible mice are more severe and often coalesce, with parenchymal collapse. Nuclei of degenerating cells often have characteristic dense, marginated chromatin or chromatin is condensed in multiple dense bodies (Fig. 114). Syncytia arising from hepatocytes or other cells can be present (Fig. 115) (Barthold 1985; Barthold and Smith 1984; Jones and Cohen 1962; Piazza 1969). In athymic nude mice, parenchymal collapse, fibrosis, and syncytium forma-