NOTE ***Pathology***

Spontaneous Aleutian Disease in a Ferret

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ABSTRACT. A 3-year-old female ferret died five days after admission to a veterinary clinic for treatment of acute dyspnea and posterior paresis. Blood chemistry showed no hypergammaglobulinemia. Histopathological examination revealed mild to severe inflammatory infiltrates, composed mostly of plasma cells, in multiple organs. Lesions were especially severe in the kidneys, where focal segmental membranous glomerulopathy was also present. In the liver, in addition to lymphocytic and plasmacytic infiltration in periportal areas, dilatation and proliferation of the bile ducts were seen. On analysis of PCR products, using primers directed against the gene encoding Aleutian disease (AD) viral capsid and formalin-fixed kidney samples, we detected a single band of about 400 bp, specific to the AD virus.—KEY WORDS: Aleutian disease, ferret, PCR.

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Aleutian disease (AD) is a persistent infection of ranch mink (*Mustela vison*) caused by a parvovirus (Aleutian disease virus (ADV)), and is an immune complex-mediated disease [2, 8]. Diagnosis of AD in mink is largely based on the presence of hypergammaglobulinemia and a high titer of non-neutralizing antibody to ADV, in addition to histopathological findings. Minks with Aleutian genotype were initially reported to be especially sensitive to the disease and to suffer a high rate of mortality, but it has subsequently been found that mink of all genotypes can develop AD [2, 8]. An ADV-specific antibody has also been demonstrated in a variety of other species, including man, fox, dog, raccoon, cat and ferret. However the only animal besides mink in which overt disease appears to occur is the ferret (*Mustela putorius furo*) [4]. Ferrets experimentally infected with the mink strain of ADV are known to develop symptoms of the disease. Spontaneous AD in ferrets has been reported in the U.S.A. [3, 6], Canada [1] and the U.K. [5, 8, 10, 11], but there has been no previous report of such spontaneous infection in Japan. This report describes the pathological and molecular biological findings observed in a ferret naturally infected with ADV.

A 3-year-old female ferret, which had been kept as a pet for two years, was admitted to a veterinary clinic with signs of acute dyspnea and posterior paresis. Symptomatic therapy was initiated, but the ferret became comatose, and died 5 days later. Results of serum chemistry on the day of admission revealed total protein 4.1 g/dL, albumin 3.4 g/dL, globulin > 1.0 g/dL, ALT 33 U/L, AST 109 U/L, BUN 31 mg/dL, creatinine 0.3 mg/dL, and glucose 104 mg/dL. A complete blood count showed RBC 4,110,000 μ/L, WBC 2,2000 μ/L and hematocrit of 21.5%. Urinalysis revealed proteinuria (3+), acidic urine (pH 5), and the presence of occult blood (3+) and urinary casts (3+). A test for antibodies to ADV was not conducted.

At necropsy, the ferret's body condition appeared good (body weight 1,060 g). The kidneys were pale and enlarged with scattered white nodules; similar nodules were seen in the liver. The lungs were edematous with ecchymoses. Mild splenomegaly and enlargement of the mesenteric lymph nodes were seen. Ecchymoses were scattered on the mucosae of the small intestines and the content of the rectum was like tar. Histopathology revealed mild to severe inflammatory infiltrates, composed mostly of plasma cells, in multiple organs, with especially severe inflammation in the kidneys (Fig. 1). Plasma cells were present throughout the renal cortex in many areas, resulting in pressure atrophy and degeneration of renal tubules. Focal segmental membranous glomerulopathy was also observed, with prominent spike formation in glomerular basement membranes (Fig. 2) and eosinophilic hyaline deposits in mesangial areas. In the liver, lymphocytic-plasmacytic infiltration in periportal areas and dilatation and proliferation of bile ducts were seen (Fig. 3). The myocardium showed degeneration and dissociation of myocytes. Plasmacytic infiltration with occasional histiocytes was also present in the lungs, meninges, choroid plexus, small intestine and pancreas. But atypia and mitotic figures were not seen in the infiltrating plasma cells (Fig. 4). Vascular lesions were slight, involving only focal hyalinization of small arteriolar walls. Other observations included hematopoeitic activation of the bone marrow, myeloid hyperplasia of the spleen and the presence of hyaline deposits in hepatocytes.

On analysis of PCR products, using primers directed against the gene encoding the ADV capsid described by Saifuddin and Fox [9] and extracts of formalin-fixed tissue from the ferret's kidneys and serum from three minks with AD as positive controls, a single band of about 400 bp specific to ADV was detected (Fig. 5).

Diagnosis of AD in ferrets has been essentially based on the same criteria as for mink. AD in mink is characterized by hypergammaglobulinemia and a high antibody titer to ADV, plasmacytic-lymphocytic infiltration in multiple organs, dilatation and proliferation of the bile ducts, global

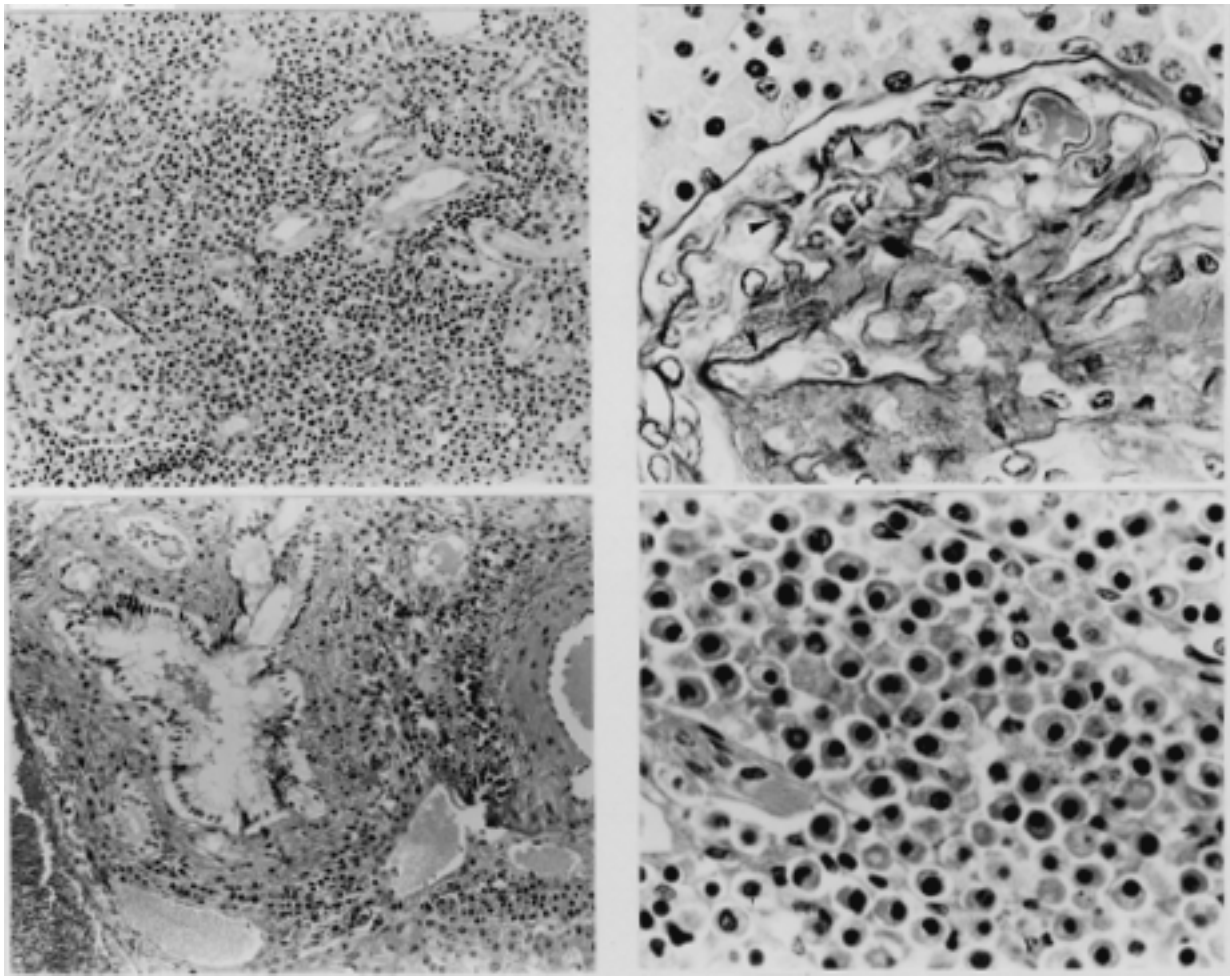

Fig. 1. Ferret kidney. HE stain. Severe lympho-plasmacytic cell infiltration in the cortex.
Fig. 2. Ferret kidney. PAS stain. Mild membranous glomerulonephritis with spike formation (arrows).
Fig. 3. Ferret liver. HE stain. Dilatation and proliferation of bile duct and mild periportal accumulation of mononuclear cells.
Fig. 4. Ferret mesenteric lymph node. HE stain. High magnification of infiltration by plasma cells.

Fig. 1	Fig. 2
Fig. 3	Fig. 4

membranous glomerulopathy and vasculitis [2, 8].

In our ferret, AD was diagnosed on the basis of histopathological lesions almost identical to those seen in mink, and identification of a band characteristic of ADV in PCR products from the ferret's kidney. However the ferret in the present study showed no hypergammaglobulinemia or vasculitis, and only focal segmental membranous glomerulopathy was present. This may relate to a discrepancy in certain features of AD between mink and ferrets that has been suggested by previous reports [4]. Hypergammaglobulinemia is considered to be pathognomonic for AD in mink. Porter *et al.* [7] reported that the levels of gamma globulin were significantly higher in ferrets with AD than in ferrets without. However, Oshima *et al.* found that only two out of 11 ferrets infected with ADV developed hypergammaglobulinemia [4]. He also suggested that AD-related membranous glomerulopathy and vasculitis in ferrets might be less severe than in mink and might sometimes be absent. If so, and if ADV-infected ferrets in fact have a lower propensity than ADV-infected mink to develop severe hypergammaglobulinemia, then the two phenomena may be related, since the clinical course of AD and the severity of lesions are believed to depend on the duration and degree of hypergammaglobulinemia [4]. The ferret in the present study, which showed no elevation in serum globulin and only focal segmental membranous glomerulopathy and an absence of vasculitis, may possibly constitute an example of this pathogenetic relationship.

Spontaneous AD in ferrets was first reported in the U.S.A. in 1967 [3] and has since been reported in Canada and U.K. [1, 5, 8, 10, 11], but this is the first report of naturally-occurring ferret AD in Japan. Results of surveys assessing latent ADV infection rates in ferrets vary from

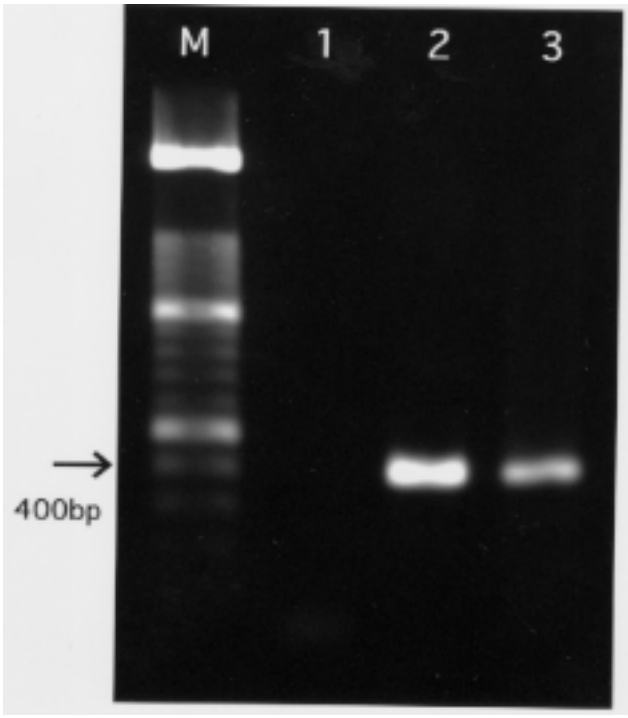

Fig. 5. Detection of Aleutian disease virus (ADV) DNA by the polymerase chain reaction method using primers directed against the gene encoding the ADV capsid. Lanes 2–3 show amplification of a 400 bp. ADV DNA fragment. M=100-bp scale molecular weight marker. Lane 1=negative control (reagent only). Lane 2= mink ADV -positive control. Lane 3= DNA from the ferret in the present case.

42% of a commercially-bred colony of 214 ferrets in the U.S.A. in 1982 [7] to just under 6% of 204 pet ferrets in the U.K. in 1990 [5], another survey found antibodies to ADV in 10% of 500 ferrets of unspecified origin [2]. However it is unknown whether the clinical disease of the ferret in the present study arose from flare-up of a latent infection or from infection newly introduced from a carrier animal, human being or object infected or contaminated with ADV.

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