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Proliferative Colitis in Ferrets: Epithelial Dysplasia and Translocation

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Proliferative bowel disease (PBD) is a common entity in pigs, hamsters, and ferrets.[1,4,5,10] In these affected species, intracellular campylobacter-like organisms (CLO) have been demonstrated within the apical portion of the hyperplastic epithelial cells. Different species of enteric campylobacter have been isolated from lesions in pigs, hamsters, and ferrets. Experimental infection with isolates of campylobacter from diseased pigs has failed to reproduce PBD consistently in conventional and gnotobiotic swine, while isolates from hamsters and ferrets have never reproduced PBD in those species.[1,2,8] The intracellular CLO in pigs, hamsters, and ferrets share a common antigen referred to as campylobacter omega antigen.[3,7] PBD has been orally transmitted to susceptible pigs and hamsters with homogenates of affected intestinal tissues from diseased animals.[5,9] Many of the features described in PBD include changes associated with neoplasia. This is not surprising since the division between hyperplasia and neoplasia is often indistinct. Changes seen in PBD include increased mitotic activity, dysplasia, anaplasia, polychromasia, loss of polarity, and hyperchromatism, as well as diverticuli of glandular epithelium that invade the submucosa and muscular tunic, often extending to the serosal surface.

Infiltration of regional lymph nodes by glandular elements containing intracellular CLO has been described in swine and in rats.[10,11] The condition in rats resembles PBD but has been termed spontaneous adenocarcinoma because glandular elements are found in regional lymph nodes. This report describes two cases of PBD in ferrets with translocation of proliferating glandular tissue to sites distal to the intestine: in one case, to the omentum and liver; and in the second, to a mesenteric lymph node.

Two ferrets, 4 months of age, were referred to our laboratory with typical signs of proliferative colitis (i.e., lethargy, rapid weight loss, and diarrhea).[4,6] Ferret 1 was placed on a 10-day regimen of oral chloramphenicol (50 mg/kg twice daily) and lactated Ringer's solution administered subcutaneously to maintain hydration. The animal's clinical signs improved with this treatment. Three weeks after cessation of therapy, biopsy of the terminal colonic mucosa was negative for the characteristic lesions of PBD. At biopsy, a palpable mass was noted in the mid-abdomen. Radiographs showed radiopaque densities in the region of the transverse colon, and an exploratory laparotomy was performed. An irregular tissue mass 5 cm in length was adhered to the omentum. The mass was located on the antimesenteric border of the intestine at the junction of the small and large intestine. A biopsy of the mass had histologic features suggestive of an adenocarcinoma with foci of bony metaplasia and extensive inflammation. Based on this finding, the ferret was killed and necropsied. Ferret 2, a female, did not receive therapy and was euthanatized and necropsied on arrival. Tissues were fixed in 10% neutral buffered formalin and processed by standard methods. Sections were cut at 5 μm and stained with hematoxylin and eosin. Selected tissues were stained by the Warthin-Starry method or trypsin-digested and prepared for immunofluorescence staining.[3,7]

At necropsy, ferret 1 had 75 cc of serosanguinous fluid in the peritoneal cavity. A mass (3 × 5 × 1.5 cm) was on the antimesenteric border of the intestine, located 15 cm proximally to the anus, and incorporated in the wall of the intestine. The omentum was tightly adhered to the tissue mass and contained multiple, firm, light-tan nodules (5–10 mm in diameter) located 1–3 cm distally to the tissue mass. A tenacious, yellow fluid exuded from cut sections of the mass and from some nodules, while other nodules contained gritty material. Mesenteric lymph nodes and the spleen were slightly enlarged. A small (1 × 3 cm), yellow mass was on the

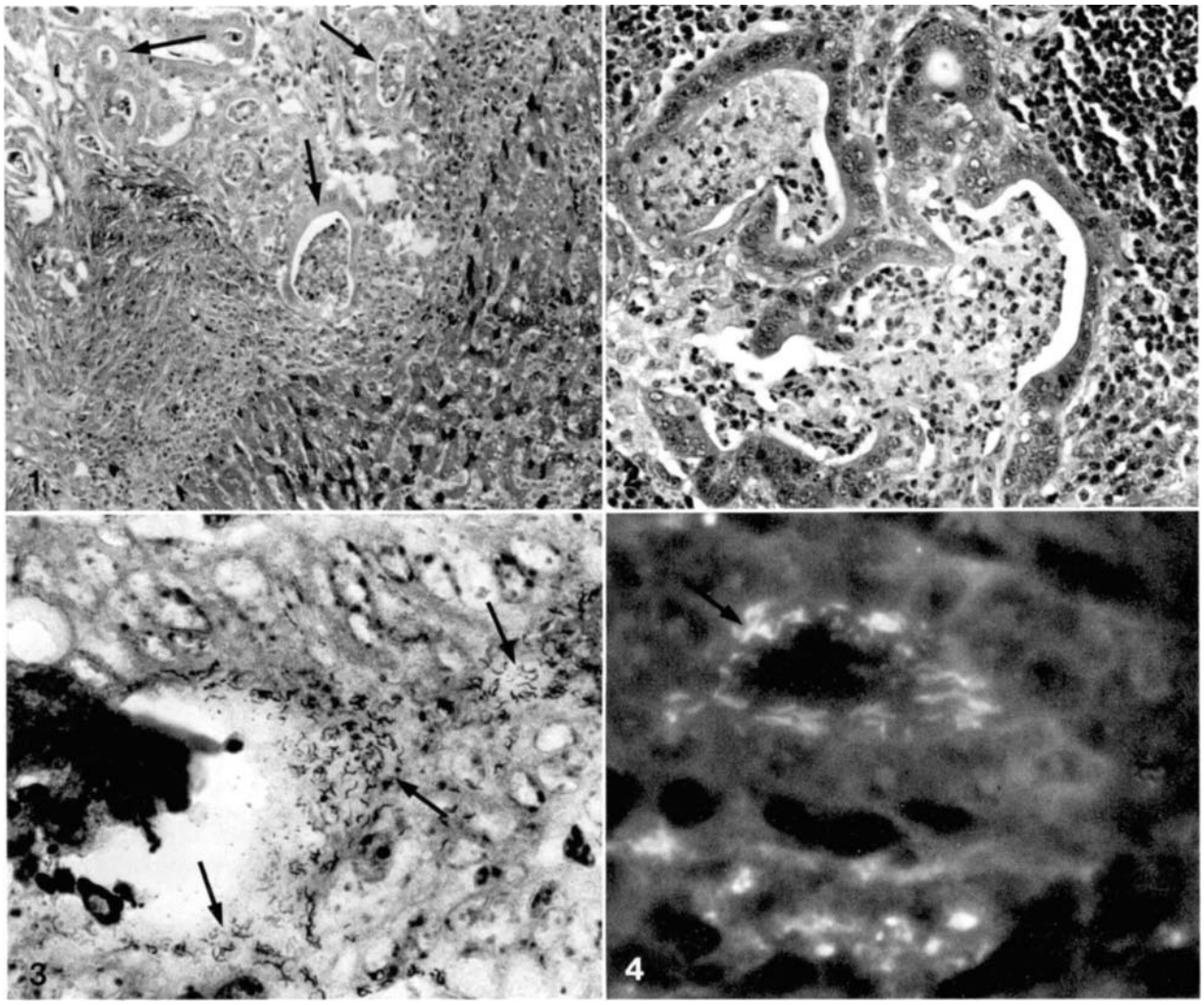

Fig. 1. Liver, ferret 1; translocated proliferative bowel disease. Glandular structures (arrows) with cell debris and inflammatory cells in lumen are separated from liver by a layer of fibrous connective tissue and inflammatory cells. HE.

Fig. 2. Mesenteric lymph node, ferret 2; translocated proliferative bowel disease. Dysplastic glands containing cell debris and inflammatory cells are lodged within a lymph sinus. HE.

Fig. 3. Mesenteric lymph node, ferret 2; translocated proliferative bowel disease showing campylobacter-like organisms (arrows) in the apical portion of glandular epithelial cells. Warthin-Starry stain.

Fig. 4. Mesenteric lymph node, ferret 2; translocated proliferative bowel disease and intracellular campylobacter omega antigen demonstrated by fluorescent antibody (arrow).

phrenic surface of the right medial lobe of liver and was adhered to the diaphragm.

The only abnormality noted at necropsy in ferret 2 was a focal (5 cm) area of thickening of the descending colon that was rough and granular on the serosal surface.

The microscopic changes in the intestine from both cases were similar and characteristic of what we have seen in numerous other cases of PBD. In ferret 1, the proliferative lesion was restricted to the portion of intestine associated with the serosal tissue mass. In ferret 2, the PBD extended from the rectum into the distal small intestine. The most extensive lesions were restricted to the thickened portion of intestine with serosal alterations. The microscopic changes in this area in ferret 2 were comparable to those seen in ferret 1. In both cases, in addition to the mucosal hyperplasia, diverticuli of glandular epithelium penetrated the muscularis mucosa and invaded the submucosa, tunica muscularis, and serosa, extending onto the external surface of the intestine. In each case, the diverticuli were accompanied by extensive necrosis and inflammation. Lesions of this nature have been seen in other ferrets with PBD.[4,6] The following changes represented a new expression of the disease process. In ferret 1, the tissue mass that involved the omentum resulted from the inflammatory process on the external surfaces of the intestine extending to the omentum. The small nodules in the omentum, distal to the mass, represented foci of translocated PBD. They

were characterized by islands of metaplastic bone, inflammatory cells, and a moderate amount of connective tissue interspersed between hyperplastic glandular epithelium. Many of the glands had neutrophils and necrotic cell debris within their lumens. The mass located on the liver had the same histologic appearance as the nodules in the omentum. This extra-intestinal focus appeared to compress the adjacent liver parenchyma but did not invade it (Fig. 1). In ferret 2, foci of glandular epithelium similar to that invading the intestinal wall were within the lymphoid sinuses of a regional mesenteric lymph node (Fig. 2). Although inflammatory cells and necrotic cell debris were present within the lumen of glands, no other evidence of inflammation accompanied these foci. Warthin-Starry stains revealed intracellular organisms in the hyperplastic glandular epithelia at the sites of PBD in the intestine and at the extra-intestinal translocated sites (Fig. 3). Fluorescent antibody staining, using polyclonal campylobacter omega antisera, confirmed the presence of CLO antigen in the epithelial cells in the proliferative bowel lesions, as well as the extra-intestinal sites of PBD in both ferrets (Fig. 4).

Metastasis is defined as the transfer of disease from one organ or part to another organ or part not directly connected. This process occurs with both pathogenic microorganisms and malignant tumor cells. This report of translocation of PBD to extra-intestinal sites in the ferret would appear to satisfy that definition since there is a transfer not only of cells but a transfer of the putative etiologic agent of PBD as well. The CLO-associated, spontaneous adenocarcinoma described in Wistar rats is similar microscopically to that of the ferret and other species that develop PBD; however, it has been designated a neoplasm.[11] In select cases of porcine intestinal adenomatosis, dysplastic epithelial cells with intracellular CLO have been reported in mesenteric lymph nodes, but in these cases were not considered neoplastic.[10] Our recent experiments with chloramphenicol therapy in ferrets, documented to have PBD by colonic biopsy, have resulted in an apparent eradication of PBD confirmed by follow-up colonic biopsy.[6] Ferret 1 did receive a regimen of chloramphenicol therapy, and necropsy findings indicated that PBD had been eliminated from all but a small segment of colon. Continued therapy in this ferret may have eliminated the lesion from the bowel and the extra-intestinal sites.

Endometriosis and translocation of placental trophoblasts to distal sites are precedents for the ability of non-malignant epithelial tissues to move from their site of origin to distant locations. Similar mechanisms may apply in PBD. Hormonal stimuli may be related to translocation of endometrial and placental tissue, whereas intracellular CLO may be responsible for initiating PBD and its translocation to extra-intestinal sites. This can be investigated further once PBD is experimentally reproduced in the ferret.

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