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PRELIMINARY OBSERVATION ON PANCREATIC DUCT ADENOCARCINOMA INDUCED BY INTRADUCTAL ADMINISTRATION OF N-ETHYL-N′-NITRO-N-NITROSOGUANIDINE IN DOGS

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Pancreatic duct adenocarcinoma was induced by intraductal administration of N-ethyl-N′-nitro N-nitrosoguanidine (ENNG) in two mongrel dogs. A dog received a total dose of 595 mg of ENNG during 12 months and was sacrificed. Duct obstruction was detected by pancreatography and duct adenocarcinoma was found. Another dog was given a total dose of 350 mg of ENNG during 8 months and was sacrificed 26 months after the first administration of the carcinogen. Duct adenocarcinoma was found. No pancreatic tumors were found in 2 dogs given intraperitoneal N-nitrosobis(2-oxopropyl)amine at a total dose of 4000 mg or in 2 dogs given Tween 60 only. These results suggest that the direct presence of a carcinogen in the pancreatic duct was able to induce duct adenocarcinoma in dogs.

Key words: Pancreatic duct adenocarcinoma — ENNG — Dog

The incidence of pancreatic carcinomas with poor prognosis in humans has been increasing.[1] For the prevention and detection of early pancreatic carcinoma, information on causal factors, histogenesis and characteristic growth behavior of experimental pancreatic neoplasms is needed. So far pancreatic carcinogenesis has been studied mainly in hamsters and rats. In the present experiment an attempt was made to produce pancreatic duct adenocarcinoma, the type with the highest incidence in humans,[2] in dogs, since this animal is a useful one in which to observe the clinico-pathological features of tumor development. This paper describes a preliminary observation of pancreatic duct adenocarcinoma induced by N-ethyl-N′-nitro-N-nitrosoguanidine (ENNG) in dogs. ENNG (Aldrich Chemical Co., Inc., Milwaukee, Wis.), a direct carcinogen which has been used to produce experimental gastric[3] and colon cancers[4] in dogs, was administered into the pancreatic duct through a pancreatic drainage tube. N-Nitrosobis(2-oxopropyl)amine (BOP) was kindly supplied by Dr. Yukio Mori, Laboratory of Radiochemistry, Gifu Pharmaceutical University, Gifu.

The dogs used in this experiment were 6 male mongrel dogs, 2 for ENNG, 2 for BOP administration and 2 controls. For the administration of ENNG, the dogs, each weighing approximately 15 kg, were laparotomized under Nembutal anesthesia and pancreatic drainage was performed by inserting a JMS cut-down tube (Japan Medical Supply Co., Hiroshima) 0.6 mm in diameter into the duct at a distance of 5 cm from the tail portion of the pancreatic duct in one dog (Case 1) and into the dorsal pancreatic duct at a distance of 5 cm from the head portion in the other dog (Case 2). After the operation, broad-spectrum antibiotics were injected for 5 days and ENNG administration was started one week after the operation. ENNG was dissolved in 1 ml of 0.4% Tween 60 and administered at a dose of 5 mg per dog through the drainage tube once or 4 times per week. BOP dissolved in 0.9% NaCl solution was injected intraperitoneally at a dose of 200 mg/body once a week for 20 weeks into 2 dogs, each weighing approximately 15 kg (Cases 3 and 4). Two dogs, each weighing approximately 14 kg

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(Cases 5 and 6), received intraductally 1 ml of 0.4% Tween 60 alone in the same manner as in Cases 1 and 2, respectively.

In Case 1, the animal was given a total dose of 595 mg of ENNG (119 administrations) for 12 months and the changes in the pancreatic duct were observed every month by pancreatography. The pancreatography was performed by injection 1–2 ml of 60% Urografin (Japan Schering Co., Osaka) into the drainage tube and taking X-ray photos with an Animal Experiment X-ray Apparatus (Toshiba Medical Co., Tokyo). Constriction was detected after 8 months. The animal was sacrificed 12 months after the first administration of ENNG by exsanguination from the femoral artery under Nembutal anesthesia. Final body weight was 12.5 kg. As shown by pancreatography just before sacrifice (Fig. 1), constriction of the pancreatic duct was apparent. The tumor was not detectable from the surface of the pancreas, but a cut section revealed a hard, whitish-gray tumor in the duct lumen. Histologically, tubular adenocarcinoma was seen in the pancreatic duct lumen accompanied with invasion to the surrounding pancreatic parenchyma through rupture of the duct basement membrane (Figs. 2 and 3). Accompanying chronic pancreatitis and a duct-like structure of the acinar cells were also seen.

In Case 2, although the tube slipped out of the pancreatic duct 8 months after the first administration of ENNG, 70 administrations of ENNG (tatal dose of 350 mg) were given during this period. The animal excreated white stools having a sour odor and was moribund 23 months after the first administration of ENNG. The dog was sacrificed in the same manner as for Case 1, at the 26th month.

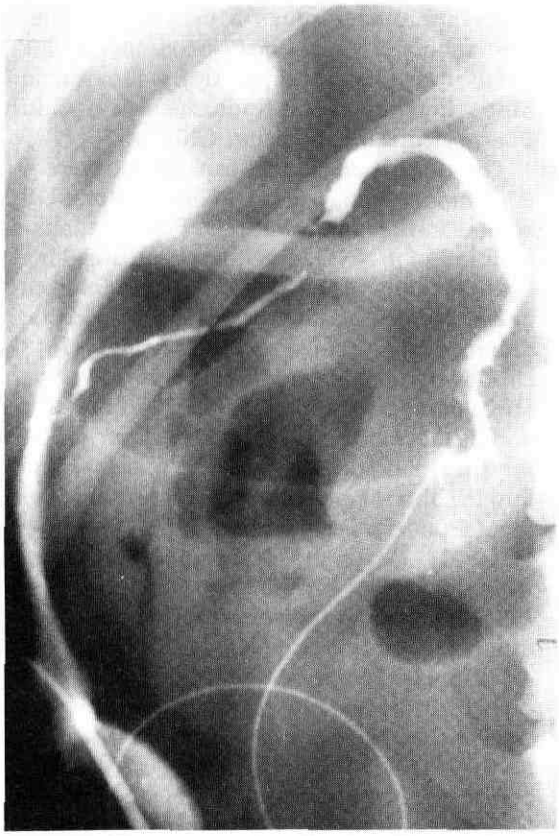

Fig. 1. Pancreatography of a dog, Case 1, showing constriction of the main pancreatic duct.

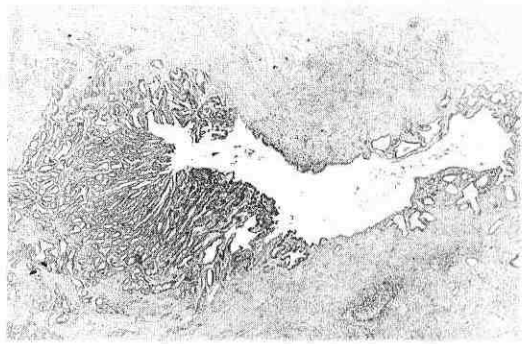

Fig. 2. Histology of tubular adenocarcinoma found in a dog, Case 1. Hematoxylin-eosin stain. ×4.

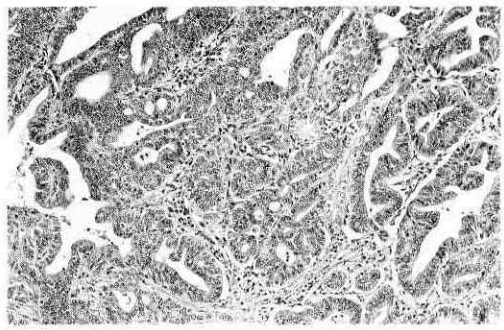

Fig. 3. High magnification of Fig. 2.

Final body weight was 12 kg. A macroscopic view of the pancreatic head tumor is schematically shown in Fig. 4 and a photograph is shown in Fig. 5. A tumor of the pancreatic head, $10 \times 11.5 \times 7$ cm in diameter, accompanied with dilatation of the common bile duct and the gallbladder, was observed together with jaundice. Histologically, the tumor was characterized as duct and ductular proliferation accompanying chronic pancreatitis. A duct-like structure of the acinar cells were also seen. This case was also diagnosed as pancreatic duct adenocarcinoma (Fig. 6). Cases 3 and 4 each received a total dose of 4000 mg of BOP, and died 8 months after the beginning of the experiment. These dogs died of hepatic failure due to liver cirrhosis and no pancreatic tumors were observed. The final body weight of Case 3 was 12.5 kg and that of Case 4 was 13 kg. Cases 5 and 6 were sacrificed 12 months after the beginning of the experiment in the same manner as Case 1. No pancreatic tumors were observed.

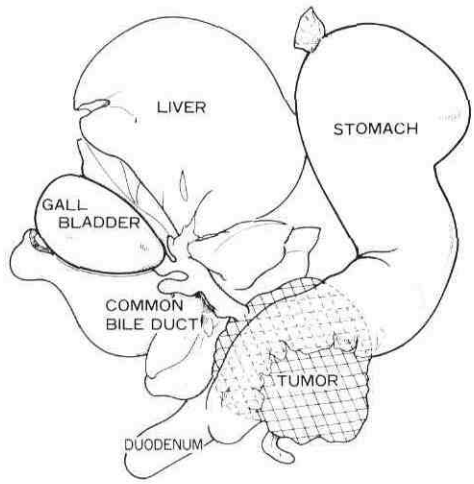

Fig. 4. Schematic illustration of Fig. 5.

There have been no reports on the induction of pancreatic duct adenocarcinoma by intraductal administration of carcinogen in dogs. Morris and Eyestone[5] reported the induction of acinar cell adenomas after oral administration of 2-acetylaminofluorene in dogs. The present study of Case 1 clearly demonstrated cancerous changes in duct epithelial cells. It has been shown previously that it is possible to induce pancreatic duct adenocarcinomas with BOP in hamster.[6] The absence of induction of pancreatic tumor by BOP in dogs might be due to a species difference in susceptibility of dogs and hamsters to BOP. However, the model of pancreatic carcinogenesis in hamsters is thought to involve a hematogeneous process, and may not occur via the pancreatic juice.[7] The present result indicate that ENNG present in the pancreatic duct of dogs induced adenocarcinomas and support the epidemiological view that some carcinogens to which humans are exposed might circulate in the pancreatic juice and induce adenocarcinoma.[8] Furthermore, the incidence of spontaneous pancreatic tumors is rare, ranging from 1.3 to 2.05% among all tumor sites in dogs.[9] The present

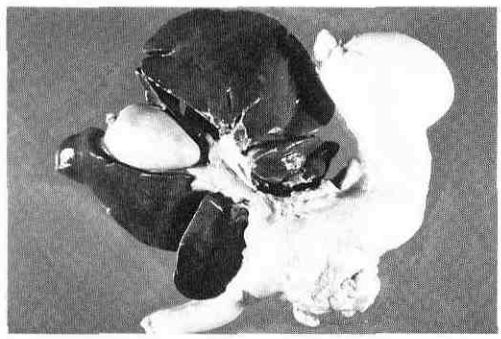

Fig. 5. Macroscopic view of pancreatic head tumor, accompanied with dilatation of the common bile duct and the gallbladder in a dog, Case 2.

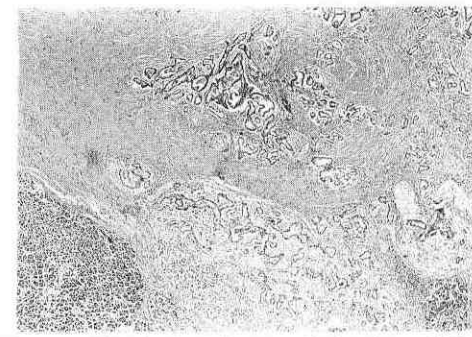

Fig. 6. Histological figures of the dog of Fig. 5 (Case 2), diagnosed as duct adenocarcinoma. Hematoxylin-eosin stain. $\times 4$.

results are therefore of considerable interest, and may help to clarify the clinico-pathological features of pancreatic duct adenocarcinoma during its development. However, additional information obtained with a larger number of dogs is required for a better understanding of this important issue.

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