



## NOTE

Pathology

# Primary intrahepatic squamous cell carcinoma in a sika deer

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**ABSTRACT.** A white nodule was detected in the liver of a wild female sika deer. The nodule was histologically diagnosed as squamous cell carcinoma (SCC), and it transitioned into a hyperplastic and chronically inflamed intrahepatic bile duct showing *Fasciola* infection. Therefore, the tumor was demonstrated to have originated from the biliary epithelium of the intrahepatic bile duct. Hyperplastic and chronic inflammatory changes of the biliary epithelium might have contributed the carcinogenesis of the present case, as proposed in human primary intrahepatic SCC cases. To the best of our knowledge, this is the first reported case of primary intrahepatic SCC in an animal.

**KEY WORDS:** *Cervus nippon yesoensis*, fascioliasis, intrahepatic bile duct, neoplasm, squamous cell carcinoma

Primary squamous cell carcinoma (SCC) of the liver is rare and has only been sporadically reported in humans [3, 5, 7, 8]. In the World Health Organization (WHO) classification of tumors of the liver and intrahepatic bile ducts (IHBDs) in humans, SCC is described as one of the histological variants of intrahepatic cholangiocarcinoma [4]. On the other hand, although a case of SCC originating from the distal part of the choledochal duct was reported in a cat, to the best of our knowledge, no cases of primary intrahepatic SCC have been reported in the veterinary literature [6]. In this report, we present a case of SCC that arose in the liver of a sika deer.

The deer involved in the present case was a wild adult female sika deer (*Cervus nippon yesoensis*), which was hunted in the northern district of Hokkaido, the northern island of Japan. The deer weighed 83 kg. At slaughter, a white nodule was detected in the liver, and the whole liver was sent to our laboratory to undergo pathological examinations. No abnormal findings were found in other organs.

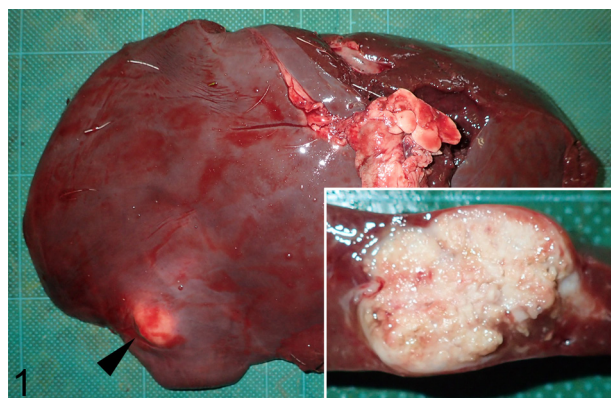
A white nodule, which measured about 2 cm in longest diameter, was located at the periphery of the left lobe of the liver (Fig. 1). The cut surface of the lesion demonstrated that it was an abscess-like nodule, containing white, homogenous, and dry material (Fig. 1 inset). Cut sections of the liver parenchyma revealed thickening and dilation of an IHBD, which ran in the vicinity of the nodule, and *Fasciola* flukes residing in the duct lumen. Liver specimens including the nodule were fixed in 10% formalin and used for histological examinations. The contents of the nodule were examined bacteriologically, but no bacteria were detected.

Histological examinations revealed that the nodule was composed of a cystic structure and was mainly lined by neoplastic stratified squamous epithelial cells, which proliferated haphazardly and projected into the lumen (Fig. 2). Keratin accumulated in the nodule lumen. Subepithelial proliferation of the neoplastic cells was also observed. The neoplastic cells were similar to the normal keratinocytes of the stratified squamous epithelium, which is composed of basal, spinous, granular, and keratinizing layers, but they presented with moderate to severe nuclear atypia, and keratinization of individual neoplastic cells was often detected (Fig. 3). Neoplastic cells with bizarre large nuclei, or multinucleated neoplastic cells were sometimes observed. Mitotic figures were frequently seen (20.3 in 10 high-power fields/2.37 mm<sup>2</sup>). The outermost part of the nodule was surrounded by a collagenous fibrous layer, but the neoplastic cells had focally invaded the adjacent liver parenchyma (Fig. 2). Lymphocytes, plasma cells, and a few neutrophils had infiltrated into the surrounding fibrous tissue and the tumor stroma. Some keratinous material, which had ruptured into the tumor stroma, had caused foreign-body reactions. In addition to the neoplastic stratified squamous epithelial cells, the cystic nodule was partially lined by a single layer of columnar epithelial cells, which was admixed with goblet cells and was accompanied by submucosal glands (Fig. 4). A transition between the columnar cells and the neoplastic stratified squamous epithelial cells was observed (Fig. 4). The columnar epithelium did not exhibit any nuclear or cellular atypia and was histologically

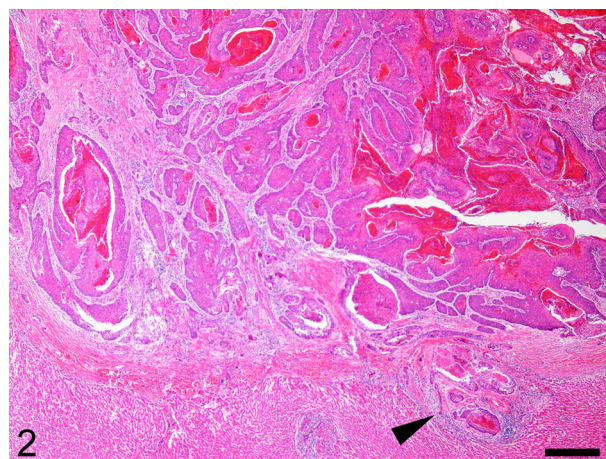
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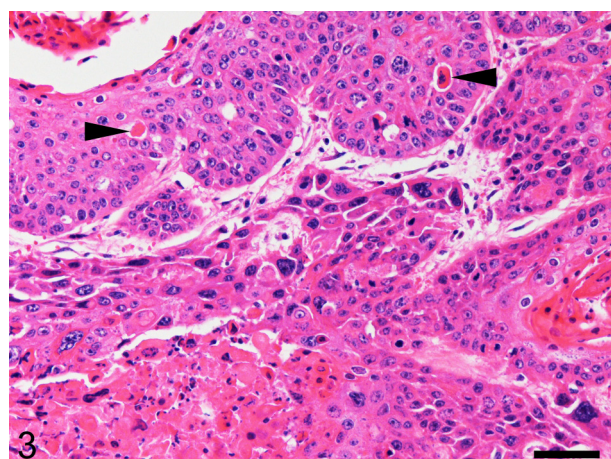
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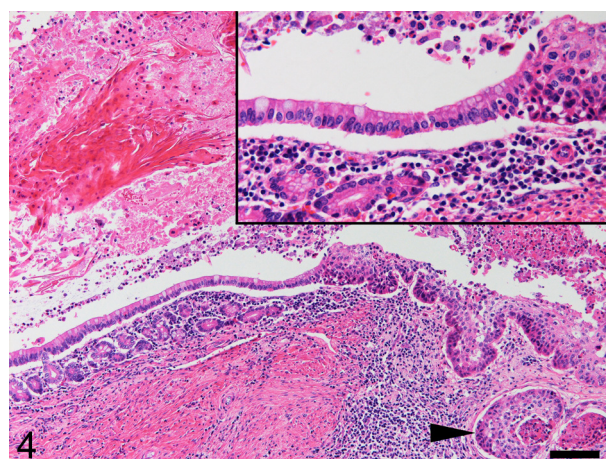
**Fig. 1.** A white nodule (arrowhead) in the left lobe of the liver of a sika deer. Inset. The cut surface of the nodule displaying white, homogenous and dry content.



**Fig. 2.** The hepatic nodule is composed of haphazardly proliferating neoplastic stratified squamous epithelial cells, contains keratin, and is surrounded by a collagenous fibrous layer. Focal invasion of the adjacent liver parenchyma by the neoplastic cells (arrowhead). Hematoxylin and eosin (HE). Bar=500  $\mu$ m.



**Fig. 3.** Higher magnification image of the neoplastic stratified squamous epithelial cells. Moderate to severe nuclear atypia and keratinization of individual cells (arrowheads). HE. Bar=50  $\mu$ m.

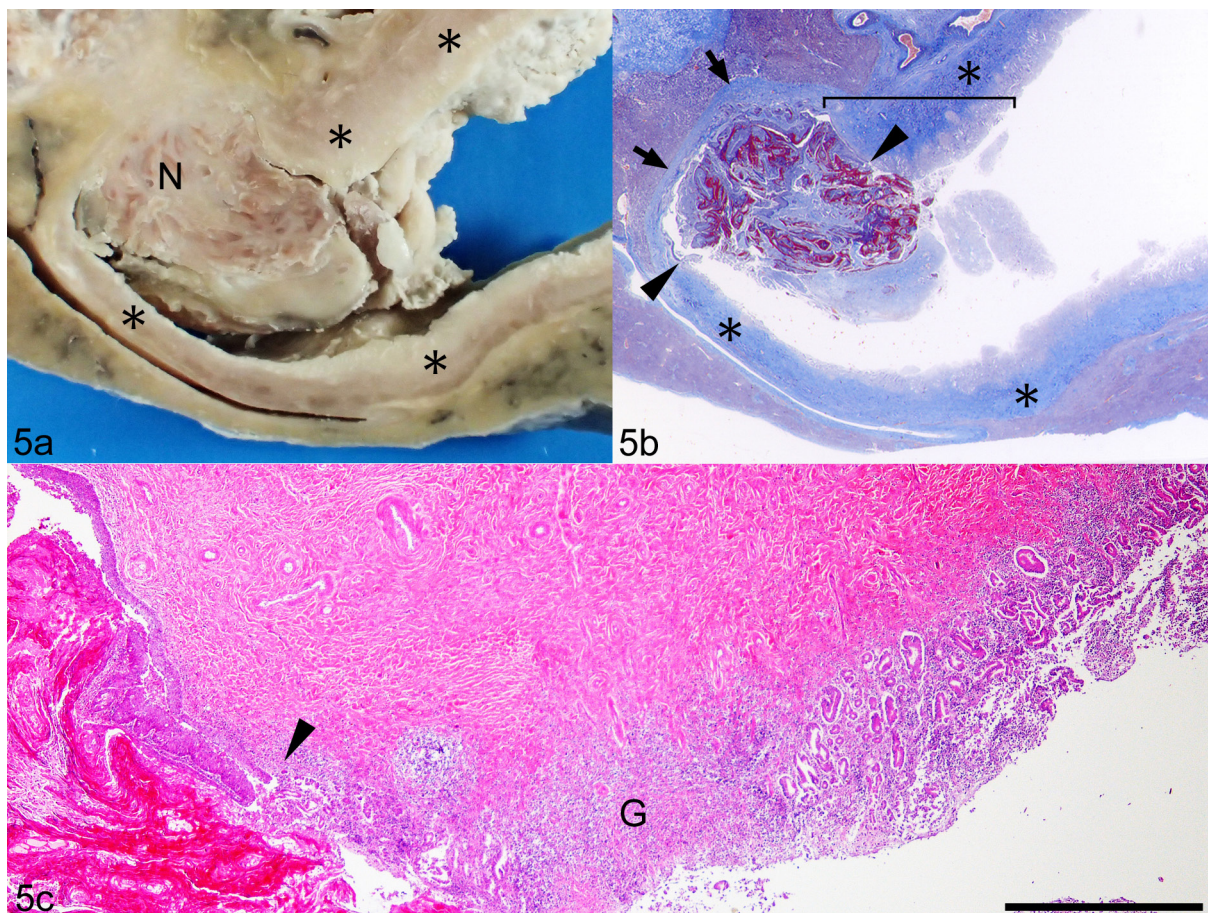


**Fig. 4.** The hepatic nodule, which is partially lined by a single layer of columnar epithelial cells admixed with goblet cells, and accompanied by submucosal glands, transitions into neoplastic stratified squamous epithelium. Subepithelial proliferation of the neoplastic stratified squamous epithelial cells (arrowhead). HE. Bar=100  $\mu$ m. Inset. Higher magnification image of the columnar epithelium showing an absence of nuclear or cellular atypia, and a sequential transition into the neoplastic stratified squamous epithelium. HE.

consistent with a non-neoplastic biliary epithelium of a large IHBD with goblet cell metaplasia. From these observations, the present case was diagnosed as SCC, and we suspected that the tumor was derived from the IHBD epithelium. The neoplastic lesion was restricted to the nodule and was not detected in anywhere else in the liver parenchyma.

To clarify the origin of the tumor, we performed additional examinations using the specimens preserved in formalin. We produced several slices that included the tumor nodule from the liver specimen, and discovered that the tumor nodule was in communication with the thickened and dilated IHBD (Fig. 5a and 5b). This was also confirmed histologically; i.e., the neoplastic stratified squamous epithelium transitioned into the hyperplastic biliary epithelium of the IHBD showing chronic inflammation (Fig. 5c). Based on these findings, we determined that the SCC originated from the biliary epithelium of the IHBD.

In humans, primary SCC of the liver has been reported to occur in association with chronic inflammation of the bile duct, congenital cysts of the biliary tract, or liver cysts associated with infections and/or stones [5, 7, 8]. Squamous metaplasia followed



**Fig. 5.** a. The cut surface of the fixed liver specimen showing the neoplastic nodule (N). Proliferating neoplastic cells project into the lumen and are in communication with a dilated intrahepatic bile duct with a thickened wall (asterisks). b. A histological section made from the liver specimen shown in Fig. 5a and stained with Masson's trichrome. The wall of the neoplastic nodule (arrows) transitions into the bile duct wall (asterisks), and the lining epithelium changes at the points indicated by arrowheads. c. Higher magnification image of the region depicted by the square bracket in Fig. 5b. The neoplastic stratified squamous epithelium transitions, at the point indicated by the arrowhead, into hyperplastic biliary epithelium, which exhibits inflammatory cell infiltration and focal granulation tissue proliferation (G). HE. Bar=1 mm.

by neoplastic transformation of the biliary epithelium under chronic inflammation has been proposed as a potential pathogenetic mechanism for hepatic SCC, but this remains to be confirmed [5, 8]. In the current deer, the hepatic SCC transitioned into the hyperplastic and chronically inflamed biliary epithelium of the IHBD showing *Fasciola* infection. Hyperplastic and inflammatory changes of the biliary epithelium were considered to be caused by *Fasciola* infection as seen in fascioliasis in other animals [2]. The current case alone was not enough to evaluate the causal relationship between *Fasciola* infection in the bile duct and carcinogenesis; however, hyperplasia and chronic inflammation associated with fascioliasis might have contributed to the carcinogenesis of the present hepatic SCC.

In the WHO classification of tumors in humans, tumors originated from intrahepatic and extrahepatic bile ducts are separated into two distinct classifications [1, 4]. In animals, a case of SCC originating from the distal part of the choledochal duct was reported in a cat, which was obviously an extrahepatic bile duct origin [6]. On the other hand, to the best of our knowledge, primary SCC within the liver parenchyma or SCC originating from an IHBD has not been reported in the veterinary literature. In the current deer case, we demonstrated that the SCC originated from the biliary epithelium of the IHBD. The present case is the first reported case of primary intrahepatic SCC in an animal.

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