NOTE *Pathology*

Glomus tumor of the liver in a cow

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ABSTRACT. An 11-year-old Holstein-Friesian cow exhibited anorexia and jaundice. A large mass was found in the liver during necropsy. Macroscopically, the mass was composed of dark red multilobular tissue and a centrally located abscess, which was connected to the hepatic duct. Histologically, the mass consisted of proliferation of small neoplastic cells and was demarcated from the hepatic parenchyma by a thick region of granulation tissue. The neoplastic cells were predominantly arranged in solid sheets, but they also formed blood-filled cancellous structures, and proliferating foci were seen around blood vessels. Periodic acid-Schiff reaction demonstrated that a fine basement membrane-like structure surrounded the neoplastic cells. Immunohistochemically, the neoplastic cells were positive for vimentin and alpha smooth muscle actin and negative for cytokeratin, factor VIII-related antigen, chromogranin and desmin. Based on its histopathological features, the hepatic neoplasm was diagnosed as a primary glomus tumor. This is the first report about a primary glomus tumor of the liver in a cow.

KEY WORDS: cholangitic abscess, cow, glomus tumor

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Glomus tumor is a mesenchymal neoplasm that originates in the neuromyoarterial glomus [18, 24]. In humans, most glomus tumors develop in the subungual region. However, they have also been reported to affect the dermis, subcutis, nerves, stomach, nasal cavity and trachea. Similarly, a few reports have indicated that primary glomus tumors can also occur in the liver [9, 10]. In veterinary medicine, glomus tumors have been reported to develop in the digits in dogs and cats [3, 7, 23], the skin in dogs and horses [1, 16, 19] and the urinary bladder in a cow [17]. Glomus tumors are typically benign, although malignant forms have been reported [1, 16]. To the best of our knowledge, no cases of primary glomus tumor of the liver or of cholangitic abscesses associated with tumors have been reported in animals.

An 11-year-old Holstein-Friesian cow was admitted to the Animal Teaching Hospital at Obihiro University of Agriculture and Veterinary Medicine with a chief clinical compliant of anorexia without fever. The cow was suspected of having nephritis due to proteinuria, hematuria and bacteriuria, which had not responded to several antimicrobial treatments. A physical examination demonstrated yellow discoloration of the visible mucous membrane and reduced ruminal motility. Blood chemistry tests detected severe hyperbilirubinemia (total bilirubin: 10.2 mg/d*l* [reference range: 0.01–0.5 mg/d*l* [21]], direct bilirubin: 5.1 mg/d*l* [reference range: 0.04–0.44 mg/d*l* [21]], indirect bilirubin: 5.1 mg/d*l* [reference range: 0–0.3 mg/d*l* [21]]), markedly elevated gamma-glutamyl transpeptidase activity (917 U/*l* [reference range: 15–39 U/*l* [21]]) and moderately increased alkaline phosphatase activity (504 U/*l* [reference range: 0–488 U/*l* [21]]). These findings were indicative of jaundice and a biliary tract disorder. Ultrasonographic imaging detected a solid mass and an abscess-like structure in the cow's liver. A reduced albumin/globulin ratio and leukocytosis (12,200/μl [reference range: 4,900–12,000/μl [21]]) and neutrophilia (9,760/μl [reference range: 1,800–6,300/μl [21]])) were also noted.

The animal was euthanized via the administration of an overdose of potassium chloride under deep barbiturate-induced anesthesia and underwent a necropsy 9 days after the first medical examination. During a gross examination, the right and caudate lobes of the liver were found to be severely enlarged. An examination of the cut surface of the enlarged area detected a well circumscribed mass (40 × 40 × 20 cm), which consisted of dark red, fragile and multilobular neoplastic tissue and an abundant bloody exudate (Fig. 1). Moreover, an encapsulated abscess (15 × 20 × 10 cm) was located in the center of the neoplastic tissue. The abscess contained a grayish-green to yellowish-white creamy caseous substance. A single dilated and thickened bile duct was observed within the neoplastic tissue, which was connected to the abscess and the hepatic duct. The hepatic duct and the intrahepatic bile ducts within the hepatic lobes had also thickened and dilated and contained various amounts of a dark green purulent caseous substance. The gallbladder exhibited pseudomembranous inflammation. A bile sample obtained from the gallbladder was subjected to a culture test for alimentary tract specimens at a human medical clinical laboratory (Kishimoto Clinical Laboratory, Tomakomai,

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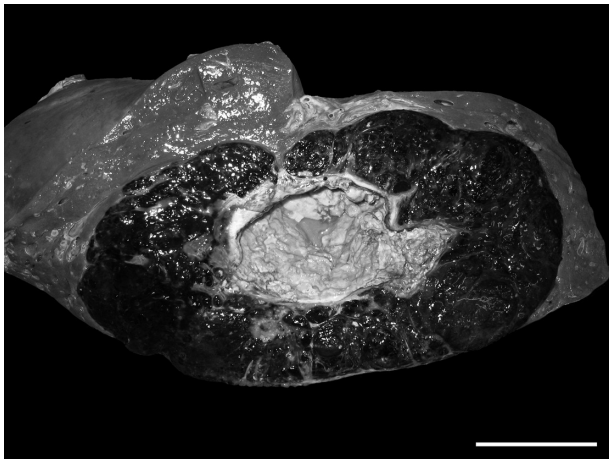

Fig. 1. Cut surface of enlarged area of the liver. Neoplastic mass and centrally located abscess within the neoplastic mass are observed. The mass is red to dark red-colored and multi-lobulated with abundant blood exudate. The abscess contains caseous materials. Bar, 10 cm.

Japan), and *Escherichia coli* was isolated from the sample. No choleliths were found in the biliary tract. There were no other significant lesions, including traumatic lesions in the alimentary tract, such as injury by metal strips, except for chronic peritonitis and jaundice.

Tissue samples were collected, fixed in 15% neutral buffered formalin, embedded in paraffin and cut into 5 μm-thick sections. The paraffin-embedded sections were stained with hematoxylin and eosin. Selected sections were stained with periodic acid-Schiff (PAS) reaction or Grimelius stain, or subjected to immunohistochemical examinations. The immunohistochemical examinations were performed using the simple stain MAX-PO polymer reagent (Nichirei Bioscience, Tokyo, Japan) after microwave antigen retrieval (20 min in 0.01 M citrate buffer, pH 6.0). The following primary monoclonal antibodies were used: anti-vimentin (Dako, Glostrup, Denmark), anti-desmin (Dako), anti-alpha smooth muscle actin (SMA) (Dako) and anti-cytokeratin AE1/AE3 (Dako). Polyclonal antibodies against anti-factor VIII–related antigen (Invitrogen, Carlsbad, CA, U.S.A.) and anti-chromogranin (Nichirei Bioscience) were also applied.

Histologically, the mass was demarcated from the hepatic parenchyma by a thick region of granulation tissue and consisted of proliferating neoplastic cells. The neoplastic cells were small and round to cuboidal in shape and had clear cytoplasm and distinct borders. The cells had distinct punched out nuclei, which were ovoid to polygonal in shape and exhibited mild anisonucleosis, and obscure nucleoli. Mitotic figures were not frequently observed; i.e., approximately 3 mitotic figures were seen in 50 high power fields (× 400). The neoplastic cells were predominantly arranged in solid sheets, although proliferating foci were seen around blood vessels (Fig. 2A), and cancellous structures containing blood filled cavities were also observed (Fig. 2B). The solid sheets of neoplastic cells gradually transitioned to cancellous structures containing blood-filled capillary-like non-neoplastic blood vessels of varying sizes. Capillary endothelial cells were occasionally observed at those blood vessels. Vascular invasion by the neoplastic cells was observed in the hepatic parenchyma near the neoplastic mass, although there were no neoplastic foci in the other organs (Fig. 2C). Special staining demonstrated that argyrophilic granules were absent. No PAS-reactive cytoplasmic substances were observed in the neoplastic cells. On the other hand, PAS reaction demonstrated that a fine basement membrane-like structure surrounded the neoplastic cells (Fig. 2D). Immunohistochemically, the neoplastic cells were positively stained for vimentin and SMA (Fig. 2E) and negatively stained for cytokeratin, factor VIII-related antigen, chromogranin and desmin.

The abscess within the mass was completely surrounded by granulation tissue, was demarcated and contained necrotic debris and bacterial clusters. Chronic suppurative cholangitis of the intra-hepatic bile duct; i.e., hyperplastic peri-ductal connective tissue and inflammatory cell infiltration (mainly involving neutrophils and lymphocytes) was widely observed (Fig. 2F). No inflammation was evident in the regions surrounding the hepatic portal vein or the intrahepatic arteries. Regions of transmural necrosis and fibrin attachment, which were admixed with numerous bacterial clusters containing cocci and bacilli, were observed in the gallbladder. Bile emboli, ductular reactions, focal parenchymal necrosis, bile extravasation and feathery hepatocyte degeneration were seen throughout the liver. As for other organs, slight non-purulent interstitial nephritis was observed in the kidneys.

The present neoplastic cells were small round to cuboidal cells with clear cytoplasm. These neoplastic cells were arranged in predominant solid sheet structures, proliferating foci around blood vessels and cancellous structures containing blood-filled cavities. Based on the predominant solid-sheet structure of the neoplastic cells and the presence of vascular structures within the tumor, neuroendocrine tumors; tumors of vascular origin; and vascular-associated tumors including glomus tumor, hemangiopericytoma and myopericytoma were considered to be possible differential diagnoses. However, the neoplastic cells lacked argyrophilic- or chromogranin-positive substances in their cytoplasm and did not express factor VIII-related antigen, which ruled out tumors of neuroendocrine or vascular origin. The pathological features of the present case; i.e., the detection of round or cuboidal cells with distinct punched out nuclei and pale to clear eosinophilic cytoplasm arranged in solid sheets interrupted by vessels of varying sizes, corresponded to those of human glomus tumors [18, 24]. In addition, the presence of neoplastic cells around blood vessels resembled the distribution pattern exhibited by glomus cells; whereas, there were no spindle-shaped neoplastic cells arranged in perivascular whorling patterns, which is a characteristic of human myopericytoma [6, 14] and bovine hemangiopericytoma [11, 13]. The immunohistochemical reactivity of the present tumor was consistent with that of human glomus tumors, which are positive for vimentin and SMA [4, 8, 12]. Based on its histopathological and immunohistological resemblance to human glomus tumors, the present neoplastic

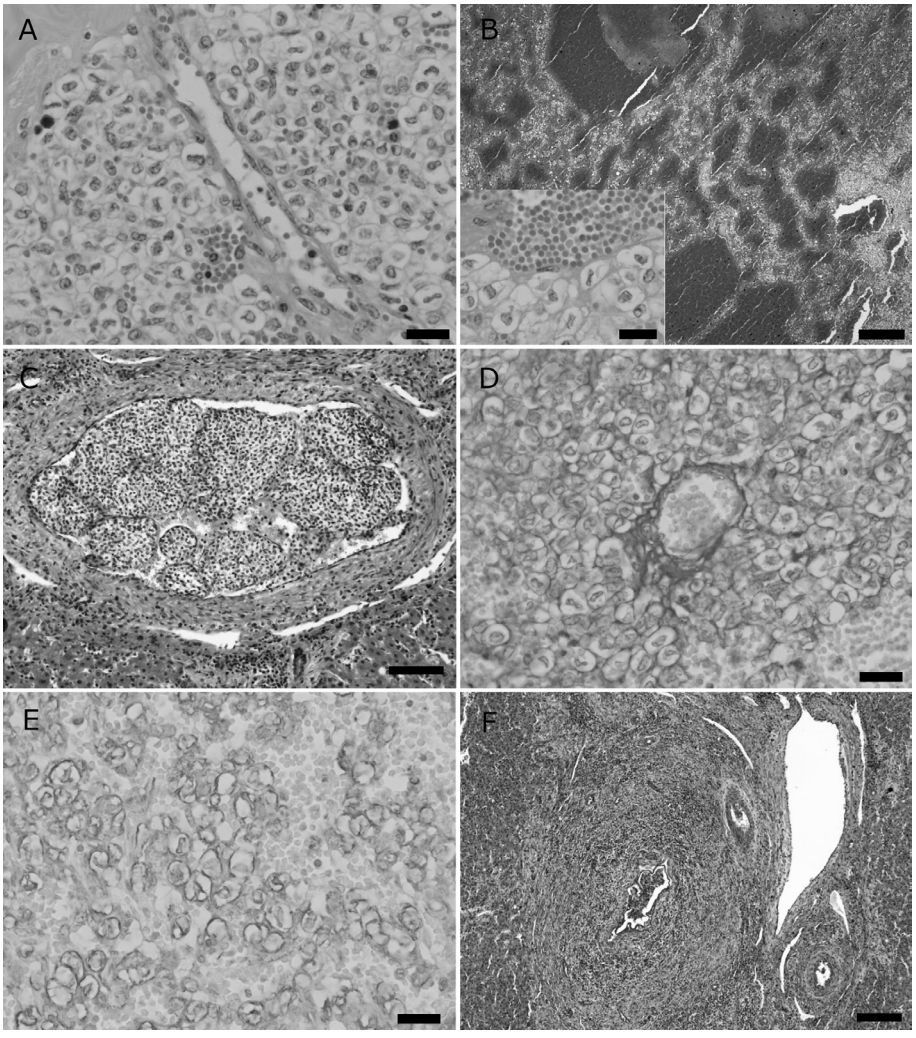

Fig. 2. A. Section from neoplastic tissue of the liver demonstrating the solid sheets of the neoplastic cells surrounding blood vessel. HE. Bar, 20 μm. B. Blood filling cancellous structure is seen in neoplastic tissue. HE. Bar, 200 μm. Inset. Higher magnification of the same area. Arrow indicates vascular endothelium. HE. Bar, 20 μm. C. The vascular invasion of the neoplastic cells was found in the hepatic parenchyma near the neoplastic mass. HE. Bar, 100 μm. D. PAS-positive basement membrane like structure finely enwraps neoplastic cell surrounding blood vessel. PAS. Bar, 20 μm. E. The neoplastic cells are positively stained with immunohistochemical staining using anti-alpha smooth muscle actin antibody as a primary antibody. Bar, 20 μm. F. Chronic suppurative cholangitis is seen in portal area. Mildly dilated biliary duct contains necrotic debris. Hyperplastic connective tissue is obvious around bile duct with infiltration of inflammatory cells and emergence of reactive small bile ducts. HE. Bar, 200 μm.

mass was diagnosed as a primary glomus tumor of the liver. In addition to the subungual region (the most common site), glomus tumors have been reported to occur at various sites in humans and animals. However, glomus tumors of the liver have not been reported in animals. Only a few reports have described human glomus tumors of the liver, and to the best of our knowledge, this is the first report about a glomus tumor of the liver in an animal. The present glomus tumor exhibited vascular invasion; however, metastatic foci were not observed despite the fact that a large mass was observed in the liver during the macroscopic examination. In humans, benign glomus tumors rarely display vascular invasion; however, such invasion is not considered to be indicative of malignancy [24]. Although further accumulation of cases is necessary, it seems that in cows, glomus tumors with vascular invasion also exhibit benign behavior.

Glomus tumors are classified into solid, angiomatous and myxoid types based on their morphological appearance [24]. Among the reported cases of glomus tumor involving animals, most lesions belonged to the solid type; however, in the only reported case of glomus tumor to involve a cow, the lesion belonged to the angiomatous type [17]. Based on its predominant solid sheet structure, the present lesion was classified as a solid type glomus tumor. Including the present report, only two cases of glomus tumor involving cows have been described. Thus, more cases of glomus tumor involving cows must be collected in order to confirm the sites at which these tumors most commonly arise, their behavior and their

histological classification. In adult cows, the major causes of liver abscesses are reported to be bacterial infection via the portal vein or a direct injury involving a foreign body [5, 15]. The biliary tract is one of the major routes of bacterial entry in cholangitis and cholangitic abscesses, especially in pigs [22]. On the other hand, cholangitis is rare in cows [2, 25], and no cases of cholangitic abscesses involving cows have been reported. Although it is possible that the cholangitis observed in the present case was caused by a descending infection, the presence of cholangitis in all hepatic lobes and the lack of inflammatory changes in the regions surrounding the hepatic portal vein and the intrahepatic arteries suggested that the cholangitis was caused by an ascending infection. The isolation of *E. coli*, a major enterobacterium, also suggested that the cholangitis was caused by an ascending infection. In humans, stenosis or obstruction of the biliary tract by a tumor can cause hepatic abscesses [20]. In addition, bile flow congestion can cause ascending infections, inflammation and secondary abscess formation. In the present case, cholangitis was widely distributed throughout the liver. The presence of a connection between the abscess and the biliary tract indicated that the abscess originated from a dilated and inflamed bile duct. Macroscopically, the abscess was limited to the tumor tissue in spite of the presence of diffuse cholangitis. It is suspected that tumors had some relationship with the abscess formation, but detailed mechanisms remain unclear.

In conclusion, the present report described a primary glomus tumor of the liver and a suspected tumor-related cholangitic abscess in a cow. Our findings suggest that glomus tumors can arise in the liver in cows.

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