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SHORT COMMUNICATION

A case of Cholangio-cellular Carcinoma in Sptiz Dog

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ABSTRACT

A 12-year-old female spitz dog was brought for necropsy to the Department of Veterinary Pathology, Ranchi College of Veterinary Science and Animal Husbandry. On gross examination, liver showed multifocal white hard nodular growths ranging from 2 mm to 1.5 cm in diameter. Both lungs showed few nodular lesions in diaphragmatic lobe. On histopathological examination, liver parenchyma showed presence of anaplastic cells distributed in lobular and multifocal ductal structures suggestive of cholangiocellular carcinoma. There was marked proliferation of fibrous connective tissue in portal area, suggesting initiation of cirrhotic changes. Microscopically, metastatic lesion of cholangiocarcinoma was observed in heart. Significant metastatic changes and venous tumor thromboemboli were also observed in lungs. Simultaneous occurrence of cholangiocellular carcinoma along with metastasis in heart is a rare condition.

Keywords: Cholangiocellular carcinoma, cirrhosis, heart, metastasis, thromboemboli

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Incidence of cholangiocellular carcinoma (CCC) along with metastasis in heart is quite rare in canines. Cholangiocellular carcinoma (CCC) is an aggressive neoplasm arising from either the extrahepatic or intrahepatic biliary tree[1]. CCC is reported as the second most common liver tumour, accounting for all malignant liver tumours[2]. The distribution patterns of cholangiocellular carcinoma in dogs are classified as massive, nodular (multiple) and diffuse forms, was reported[2]. The rate of extrahepatic metastasis has been reported to be as high as 88%, with metastatic foci frequently developing in the lungs, regional lymph nodes and peritoneal cavity[3].

A 12-year-old female spitz dog was brought for necropsy to the Department of Veterinary Pathology, Ranchi College of Veterinary Science & Animal Husbandry with a history of non-specific clinical signs like anorexia, weight loss, azotemia and right hind limb lameness.

Hematological examination of the dog was suggestive of anemia with hemoglobin level of 6 g/dl and lowered packed cell volume (20%). Neutrophilic leucocytosis was observed with Total Leukocyte Count of 31200/mm^3 and 84% neutrophils with absolute neutrophil count 26,208/cm. Biochemical examination revealed elevated Alkaline Phosphatase (ALP) 1267 U/L, Aspartate Transaminase (AST) 93.56 U/L, Alanine Transaminase (ALT) 425I U/ml. Azotemia was evident with elevated blood urea (153.59 mg/dl) and serum creatinine (3.84 mg/dl), indicative of hepato-renal dysfunction.

Most cases of CCC in canines have documented elevations in serum ALP, AST and ALT activities. Less common findings during CCC include hypoalbuminemia, hyperbilirubinemia and elevated serum bile acids, which is suggestive of decreased hepatic function and/or post-hepatic cholestasis[1].

Necropsy revealed poor body condition with generalized reduction in muscle mass. On external examination, the visible mucous membranes were icteric. All organs were critically examined and tissues were collected in 10% Neutral Buffered Formalin (NBF), processed routinely and embedded in paraffin. Paraffin sections of 3-5 µm thickness were routinely cut in rotary microtome and stained with Hematoxylin and Eosin.

Grossly, liver appeared hard in consistency with multifocal white nodular growths ranging from 2 mm to 1.5 cm in diameter. At places, large confluent lesions were noticed (Fig. 1). Histopathology of tumor lesion in the liver revealed the presence of anaplastic cells distributed in a lobular pattern with interspersed fibrous connective tissue along with presence of multifocal ductal structures (Fig. 2). The lining epithelial cells of ductular structures manifested atypical changes suggestive of cholangiocellular carcinoma. In addition, marked proliferation of fibrous connective tissue was observed in portal area, suggesting initiation of cirrhotic changes. Anaplastic/atypical changes were characterized by proliferating neoplastic cells of

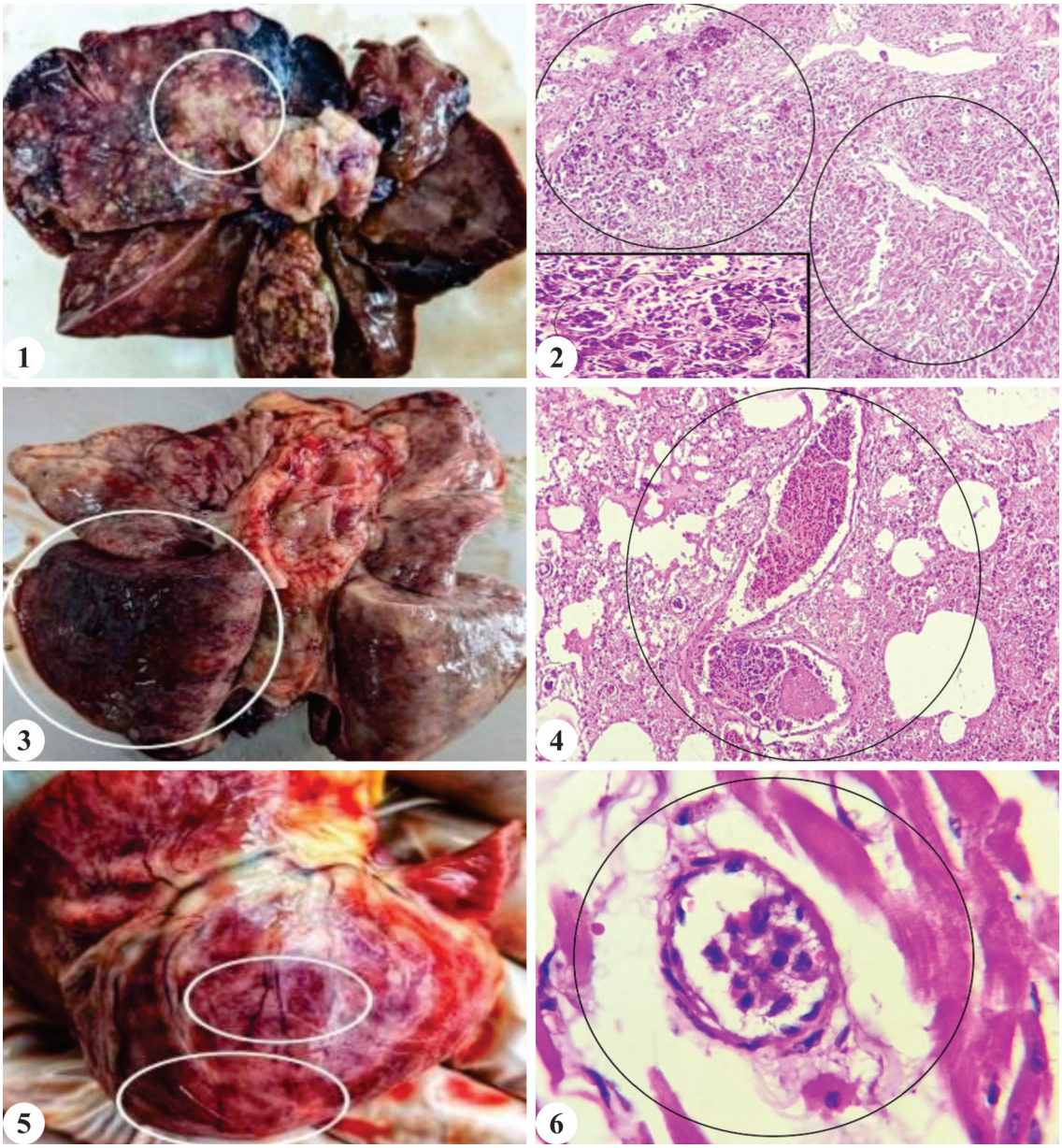

Fig. 1. Large confluent lesion in the liver; **Fig. 2.** Liver (Left circle) - Proliferating neoplastic cells of CCC with vague ductular morphology (H&E x100), (Right circle) - Atrophy of hepatocyte with dilated sinusoid space (H&E x100) and Rectangular box (Inner circle) - Pocket of neoplastic cell of Cholangiocellular carcinoma (H&E x400); **Fig. 3.** Lungs grey-red - Mottled appearance with neoplastic lesion, especially in the diaphragmatic lobe; **Fig. 4.** Lungs - Cells showing metastatic changes and venous tumor thromboemboli (H&E x100); **Fig. 5.** Rounding appearance of heart with mottled appearance; **Fig. 6.** Heart - Metastatic tumor (H&E x1000).

CCC with vague ductular morphology. Malignant bile duct epithelium showing disruption and invasion of adjacent hepatocytes. CCC has previously been reported to consist of widespread multinodular, umbilicated masses with a firm texture due to extensive necrosis and an intense scirrhous or desmoplastic response[1]. Lungs showed mottled appearance with few prominent nodular lesions in diaphragmatic lobe (Fig. 3). Histopathology of lungs also showed metastatic changes along with venous tumor thromboemboli observed in lungs with infiltrating tumor cells in the lungs interstitium suggestive of metastatic changes along with marked interstitial pneumonia and alveolar emphysematous changes (Fig. 4). Most of the blood vessels in visceral organs were packed with leukocytes. Tumor emboli in the dilated vein with seeding of tumor cells (malignant cholangiocytes) with glandular differentiation in the lung parenchyma. Marked hemorrhage in lung parenchyma with highly congested and dilated alveolar capillary. Significant fibrous exudate was observed in alveolar space. Cholangiocytes in lung parenchyma revealed atypical cellular changes. Significant eosinophilic

infiltration observed on alveolar space alongside mononuclear cell infiltration. Focal area of metastatic tumor cell proliferation also observed.

Heart was dilated having rounded appearance, mild hemorrhages were present on the epicardium (Fig. 5). Myocardium was pale in appearance. Histopathologically, a foci of metastatic cholangiocellular carcinoma in heart was observed which is a rare site for metastasis (Fig. 6) degenerative and infiltrative changes were observed. Grossly, the mucosal surface of stomach showed hemorrhages with presence of multifocal ulcers measuring about 1-2 mm in diameter. Sub adventitia revealed hemorrhage and marked congestion of anterior vein and capillaries. Villi epithelium showed degenerative changes and cloudy swelling along with necrosis. Fusion of entire length of villi giving it a continues look. Blood vessels of lamina propria were dilated and congested. Crypt showed necrosis and degeneration. Kidney appeared shrunken with irregular surface and adhesion of capsule. Capsule peeled off easily. Histopathologically, kidney showed marked necrotic and degenerative changes of renal epithelial cells. Segmental degenerative changes were also observed in glomeruli. Nephrosclerotic changes with interstitial fibrosis was evident. Spleen showed the presence of multiple red infarcts on the margins. Microscopically, spleen had mononuclear cell infiltration many of which showed deposits of hemosiderin. Histological changes in the liver were suggestive of frank cancer of CCC with metastatis in lungs and heart.

Dog was anemic due to neoplastic condition. It is anemia of chronic inflammation due to persistent immune stimulation and inflammatory cytokines (ex.IL-6) inhibiting erythropoiesis[5]. Also, GI ulcers seen in stomach may have led to chronic blood loss. Enlarged spleen with infarct and hemosiderin deposit suggests increased red cell destruction or polling. Paraneoplastic leukocytosis can produce cytokines like G-CSF (granulocyte colony stimulating factor) stimulating neutrophil production[4]. Extensive tumor necrosis and tissue damage instigate an inflammatory response. Liver tumor disrupts hepatocellular and biliary architecture releasing enzymes. ALP is significantly elevated in biliary obstruction and cholestasis (prominent in CCC). ALT/AST was elevated due to hepatocellular injury or necrosis. Ductular proliferation and fibrosis may impair bile flow. Cancer-related cachexia and anorexia, lead to prerenal azotemia[5].

Biliary epithelial cells undergo genetic and epigenetic alterations in regulatory genes, which accumulate and lead to the activation of oncogenes and the dysregulation of tumor suppressor genes (TSGs)[6]. Malignant transformation of cholangiocytes arises against a background of chronic inflammation of liver which causes repeated cycles of repair and damage which increases the likelihood of mutation in genes like KRAS and P53[7]. Damaged cells release cytokines like IL-6, TNF-alpha, which activate the immune system, causing chronic inflammation. IL-6 increases expression of progranulin, a precursor protein for granulins (a family of peptides that regulate cell growth) resulting in activation of the PI3K (phosphoinositide 3-kinase) pathway which mediates cell survival, mitosis, migration and angiogenesis[8].

TGF-beta from damaged cells, activate hepatic stellate cells present in the space of Disse, which differentiate into myofibroblast, produce extracellular matrix and cause fibrosis[9]. Fibrosis along with chronic inflammation causes cellular hypoxia. Bile duct epithelium undergoes dysplasia, decrease E- Cadherin, cause motility of tumor cells and causes invasion. Hypoxia inducible factor-1alpha (HIF-1alpha) release vascular endothelial growth factor (VEGF) which further causes angiogenesis[10]. Metastasis along with tumor causes systemic inflammation, multi-organ failure, cardio-respiratory failure and finally death.

This case adds to the limited veterinary literature on cholangiocarcinoma (CCC) in canines, especially regarding its metastatic patterns and histopathology.

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