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Diagnostic imaging of a mass-shape hepatic steatosis in a dog treated with chemotherapy

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Abstract: A left medial liver mass was found through the monitoring of the metastasis in a 15-years-old, spayed female Maltese dog. The patient had a history of chemotherapy with carboplatin after surgical resection of the mammary gland tumour. Ultrasonography (US) showed a massive hyperechoic mass in the left liver. The left medial liver mass was identified as a poorly demarcated, hypoattenuated area on the non-enhanced and all the phases of contrast-enhanced computed tomography. The liver mass was surgically removed and the histopathological examination showed a fatty deposition and no evidence of neoplasm. Based on the patient's history, diagnostic imaging and histopathological findings, the liver mass was considered as a chemotherapy-induced hepatic steatosis. This report provides the diagnostic imaging characteristics of the hepatic steatosis that could help differentiate it from a malignancy in a dog treated with chemotherapy.

Keywords: chemotherapy; diagnostic imaging; dog; hepatic steatosis; mass shaped

Hepatic steatosis is defined as the excessive accumulation of fatty acids in the form of triglycerides in the cytoplasm of the hepatocytes (Brown et al. 2017). The term steatosis tends to be used interchangeably with lipidosis and fatty change (Cullen and Stalker 2016). In dogs and cats, hepatic steatosis is associated with obesity, diabetes mellitus, prolonged fasting, congenital portosystemic shunts (PSS), endocrinopathy and toxic liver injury (Van Winkle et al. 2006; Hunt et al. 2013; Van den Bossche et al. 2017). Typically, diffuse parenchymal change is a common type of hepatic steatosis in dogs and cats (Gaschen 2009). Hepatic steatosis, one of the most common liver abnormalities in humans, has two types: alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) (Day 2006; Yeh and Brunt 2014). As the overuse of certain drugs is one of the relatively common conditions associated with NAFLD, it is difficult to distinguish the heterogeneous NAFLD from a metastatic lesion in chemotherapy patients (Maor and Malnick 2013; You et al. 2017). This report provides the diagnostic imaging characteristics of a hepatic steatosis that differentiate it from a malignancy in a dog treated with chemotherapy.

Case description

A 15-year-old, spayed female, Maltese dog weighing 3.5 kg was presented with mammary gland masses. A mass of about 3 cm in diameter was found in the fourth teat on the right-hand side, and three very small nodules were identified in its surrounding. The patient had a body condition score of 3/9 and no history of endocrine diseases. Abnormalities were not identified in the screening examinations, which included the haematology, biochemistry, thoracic radiography, and echocar-

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diography, except for a minimally increased alanine aminotransferase (ALT) [2.125 μkat/l, Reference interval (RI): 0.17 μkat/l to 2.15 μkat/l]. The abdominal ultrasonography (US) that was performed to determine the cause of the minimally increased ALT did not show any particular findings also. The dog had a bilateral mastectomy and received six cycles of chemotherapy with a 15-minute intravenous dose of 300 mg/m^2 carboplatin (Neoplatin; Boryung Pharmaceutical, Seoul, Republic of Korea) every three weeks because the mass was diagnosed as a solid type carcinoma with grade 2 malignancy according to the histopathological examination.

During the chemotherapy periods, there was a mild decrease in the white blood cells (WBC) (3.16×10^9/l, RI: 5.05 to 16.76×10^9/l) during the 3rd cycle of the chemotherapy and a mild increase in the WBC (26.16×10^9/l) during the 5th cycle, the values returned to a normal range shortly afterwards. However, there was a moderate increase in the ALT (7.667 μkat/l) and alkaline phosphatase (ALP) (9.435 μkat/l, RI: 0.391 μkat/l to 3.604 μkat/l) right after the last cycle of the chemotherapy. Temporary liver toxicity caused by the chemotherapy was suspected, but the liver enzymes were back to a normal range a month later.

However, monitoring the metastasis using abdominal US revealed a large heterogeneous hyperechoic mass that had not been identified in the left liver before the chemotherapy. The mass showed irregular margins and a more increased echogenicity than the spleen. The parts with the increased echogenicity in the mass showed a fine echotexture, and the walls of the portal veins were obscured due to the increased parenchymal echogenicity (Figure 1). The left medial liver mass – exactly 4.4 × 4.3 × 3.0 cm in size – was identified as a poorly demarcated, heterogeneously hypoattenuated area than the other liver parenchyma on the non-enhanced and all the phases of the contrast-enhanced computed tomography (CT). On the non-enhanced CT, the average attenuation value of the normal liver parenchyma was about 50 Hounsfield units (HU) and the attenuation of the liver mass was from −10 HU to 20 HU. Even some parts in the liver mass were identified as having lower attenuation than the blood vessels of the liver and gallbladder on the non-enhanced CT (Figure 2). There were no findings associated with the PSS and metastasis to the other organs on the CT. The liver mass, which had a heterogeneous yellow colour and an extruded shape, was surgically removed through a laparotomy. The histopathological examination showed that most of the hepatocytes had large vacuoles, which were stained red in colour with Oil Red O Staining and identified as a lipid component. These findings were indicative of hepatic steatosis and there was no evidence of neoplasm (Figure 3).

Based on the patient's history, diagnostic imaging and histopathological findings, the liver mass was considered as a chemotherapy-induced hepatic steatosis. The dog has now been clinically healthy for 18 months since its discharge and has not shown any abnormalities in the liver enzymes and the liver US.

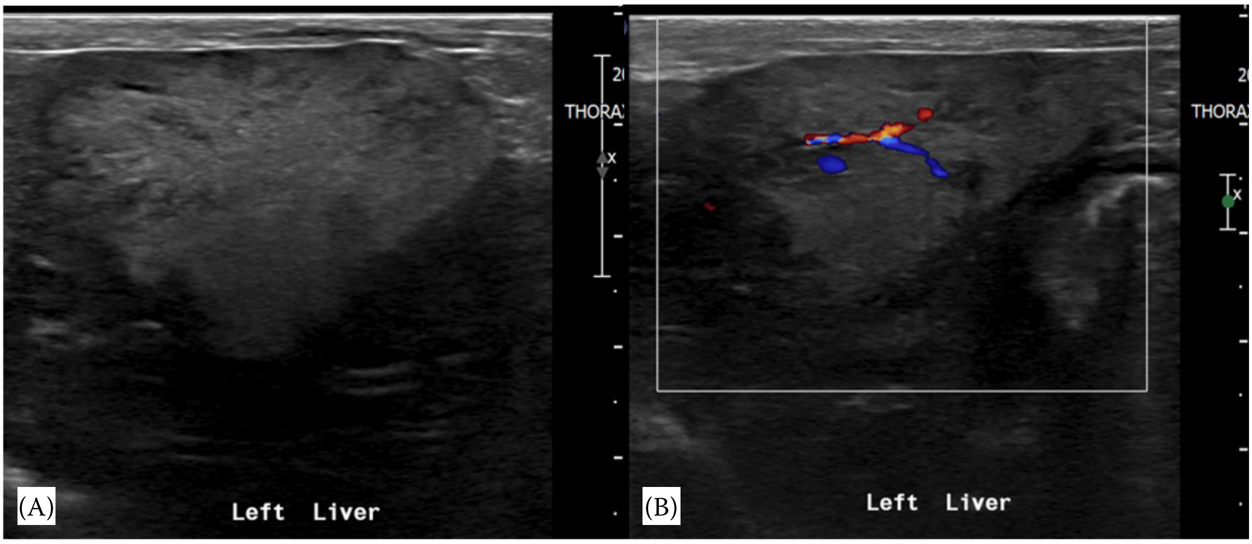

Figure 1. The ultrasonographic images of the left liver mass. The mass shows an irregular margin, a more increased echogenicity than the other liver parenchyma (A) and no vascular distortion (B)

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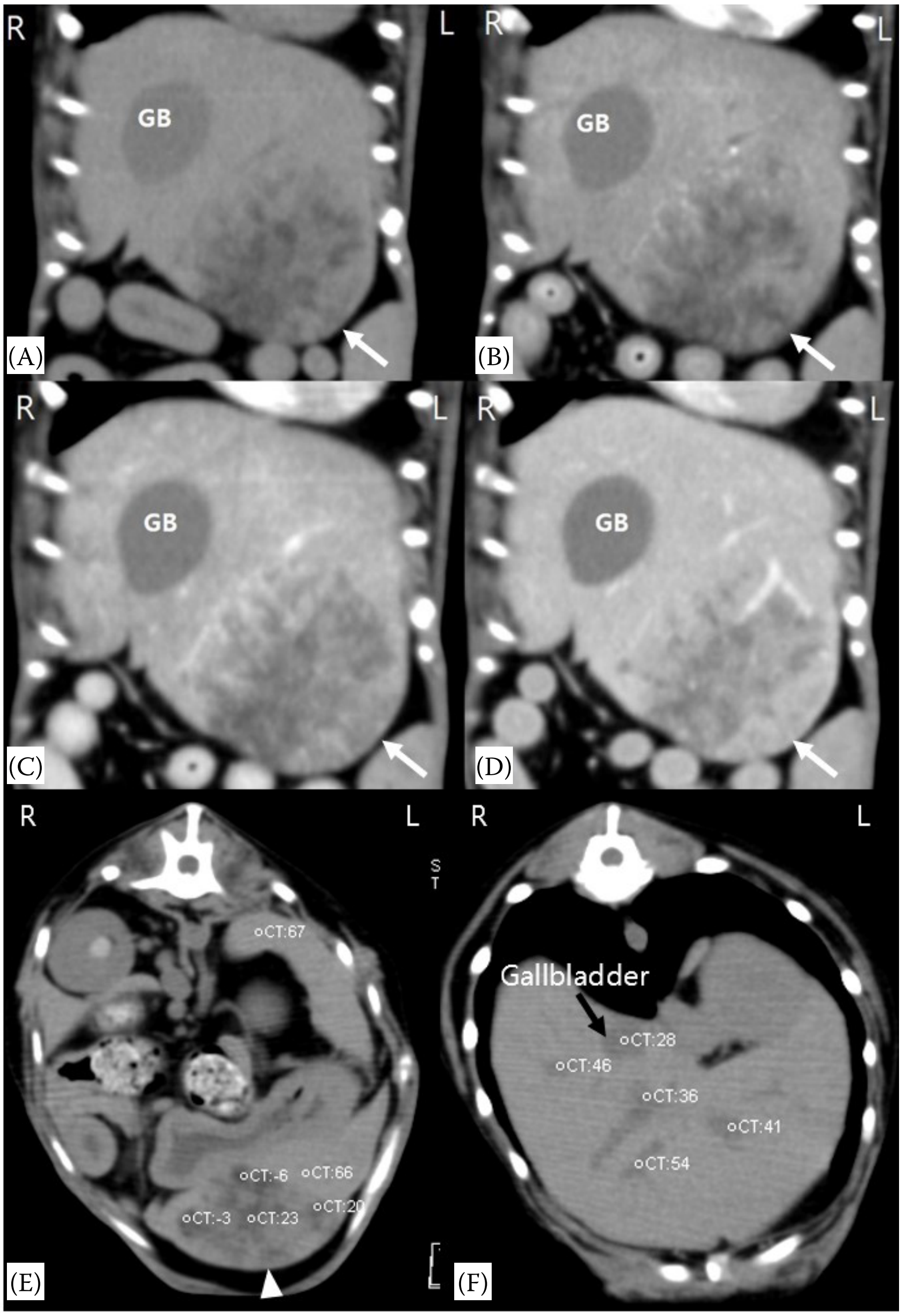

Figure 2. The dorsal plane reformatted computed tomographic (CT) images of the mass (A-D, white arrows). A left medial liver mass of about 4.4 × 4.3 × 3.0 cm in size is identified as a poorly demarcated, heterogeneously hypoattenuated area than the other liver parenchyma on the non-enhanced (A) and all the phases of the contrast-enhanced CT (B: aortic phase, C: portal phase, D: delayed phase). The transverse image of the mass (E) and normal side of the liver (F) on the non-enhanced CT. The liver mass (arrow head) is hypoattenuated more than the normal liver parenchyma, and the attenuation of the mass is from a negative to positive 20 HU (E). Some parts in the liver mass are identified as having a lower attenuation than the blood vessels of the liver and gallbladder (F)

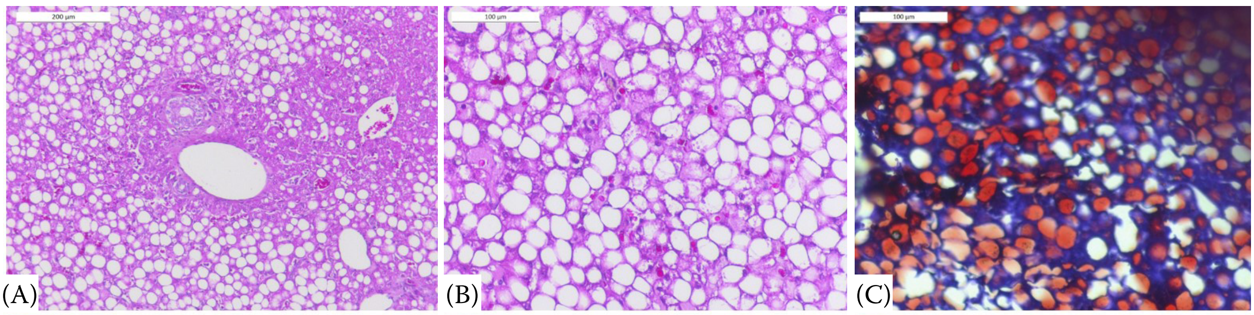

Figure 3. The histopathological examination of the mass show that most of the hepatocytes have large vacuoles (A, B). The large vacuoles in the hepatocytes stain in red colour with Oil Red O Staining (C)

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DISCUSSION

As the liver plays a central role in drug metabolism and clearance, most chemotherapy drugs can induce liver toxicity which ranges from asymptomatic mild abnormalities on the blood work to an ill-appearing patient with significant liver damage (Sharma et al. 2014).

Hepatic steatosis is the most common form of response to liver cell damage (Kalil et al. 2014). The 5-fluorouracil, platinum derivatives and taxanes of the chemotherapy drugs are known to lead to hepatic steatosis in human medicine (Sharma et al. 2014). The carboplatin used in the present case was a platinum-based drug, whose major side effects include nephrotoxicity and myelosuppression (Hume et al. 2009; Oun et al. 2018). Since other platinum-based drugs can cause hepatic steatosis and carboplatin-induced liver failure has been reported in human medicine (King and Perry 2001), the carboplatin was highly likely to the cause hepatic steatosis in the dog. Although there have been no reports about carboplatin-induced hepatic steatosis in dogs, the liver mass was considered as a chemotherapy-induced hepatic steatosis because the dog was not overweight and had no endocrine diseases or congenital PSS that could cause the hepatic steatosis, and more importantly, because the mass was not identified before the chemotherapy.

Chemotherapy-induced hepatic steatosis is generally a macrovesicular steatosis (Rabinowich and Shibolet 2015). The histopathology of the liver mass in this case also revealed a macrovesicular steatosis. Microvesicular steatosis, on the other hand, is more common in uncontrolled diabetes mellitus and feline fatty liver syndrome and can be a hallmark of a more severe hepatic dysfunction than a macrovesicular steatosis (Cullen and Stalker 2016). In addition, macrovesicular steatosis tends to be more yellow and enlarged than a microvesicular steatosis (Cullen and Stalker 2016).

It is considered that this was why the local hepatic steatosis appeared as a mass form instead of a diffuse form. In human medicine, the distribution of a hepatic steatosis can vary from diffuse infiltration to focal steatosis (Sharma et al. 2014). However, to the authors' knowledge, detailed reports on a focal or mass type of hepatic steatosis have not been previously described in the veterinary literature.

Since an atypical hepatic steatosis – not the diffuse type – can be easily misdiagnosed as a malignancy, diagnostic imaging is useful for diagnosing a hepatic steatosis (Vilgrain et al. 2013). On the US, the hepatic steatosis is hyperechoically compared to the spleen, with a loss of definition in the diaphragm and the poor delineation of the intrahepatic vessels in the lesions (Hamer et al. 2006; Decarie et al. 2011). A colour Doppler examination generally does not show mass effects or vessels (Hamer et al. 2006; Gaschen 2009; Decarie et al. 2011). The liver mass of the dog, in this case report, showed most of the characteristics of a hepatic steatosis on the US.

In human medicine, the non-enhanced CT attenuation of a hepatic steatosis is lower than 40 HU or at least 10 HU lower than that of the spleen (Hamer et al. 2006; Decarie et al. 2011). In severe cases, hepatic steatosis lesions may appear hypoattenuated relative to the intrahepatic vessels (Jain and McGahan 1993). In veterinary medicine, two CT studies of hepatic steatosis have been reported, which observed a diffuse distribution and negative hepatic attenuation values (Heo et al. 2018; Carloni et al. 2019). However, unlike other veterinary studies, the hepatic steatosis, in this case, had a mass shape and showed a wide range of attenuation from negative to positive values at 20 HU.

In human medicine, a hepatic steatosis may be more diverse in form, including diffuse, geographic, focal, subcapsular, multifocal or perivascular hepatic steatosis (Rabinowich and Shibolet 2015). While it is not difficult to diagnose a diffusely involved hepatic steatosis by using US and CT only, it is not easy to diagnose atypical heterogenous forms of steatosis on US or CT as they may mimic a malignancy (Rabinowich and Shibolet 2015; Heo et al. 2018). In this case, the mass was more likely to be a metastatic lesion from malignant mammary tumours or a primary hepatic tumour than the liver toxicity caused by the tumour chemotherapy because it had an atypical mass shape and showed heterogeneous attenuation.

Chemotherapy-induced hepatic steatosis is often reversible if the chemotherapy is discontinued (King and Perry 2001; Rabinowich and Shibolet 2015). Therefore, it is recommended to monitor the lesions if the symptoms are not serious and the liver enzyme concentrations are not severely increased. Considering the fact that the patient showed no particular clinical symptoms and its liver enzyme

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concentrations were not high, it would seem that monitoring would have been a better recommendation than the surgical removal. Still, a severe hepatic steatosis can progress to cirrhosis of the liver and requires the surgical removal in some cases (Reddy et al. 2014; Rabinowich and Shibolet 2015).

In conclusion, an atypical form of hepatic steatosis that is not diffusely involved can be misdiagnosed as a malignancy. Diagnostic imaging, such as US and CT, is useful for diagnosing liver steatosis. To the authors' knowledge, this is the first case report of a mass-shaped hepatic steatosis caused by chemotherapy in dogs.

During the chemotherapy in dogs, if the liver lesion appears to be hyperechoic on the US and hypoattenuated on the non-enhanced and all the phases of the contrast-enhanced CT, a hepatic steatosis should be considered even if it has the shape of a mass.

Conflict of interest

The authors declare no conflict of interest.

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