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Study on Liver Neoplasia in Shih Tzu Dog: A Case Report

(LAPORAN KASUS: STUDI LIVER NEOPLASIA PADA ANJING SHIH TZU)

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ABSTRACT

Liver neoplasia is the excessive and uncontrolled replication of hepatocytes that forms nodules can visible in ultrasonography. The study was purposed to study and discuss the characteristic, diagnosis and treatment of liver neoplasm through the interpretation of ultrasonography and hematology in a Shih Tzu dog. Ultrasonography is conducted with a Chison Q8 ultrasound machine with a 5-7 MHz frequency convex probe on lateral recumbency. The blood cells, liver enzymes and nodules sizes were the main parameters in this study. The results in the period of three years from 2021-2023 were interpreted and supported with secondary data sources. The Shih Tzu dog is 14 years old in the year 2023 with a body weight of 5.21 kg. No obvious clinical signs were observed during previous examinations. However, lethargy, vomiting and anorexia were recorded in its latest examination. Thrombocytosis, granulocytosis, high liver enzymes and hypoglycemia, which are some of the neoplastic clinical manifestations, were also presented by this patient. Besides, liver neoplasm, spleen neoplasm and biliary sludge were seen in the sonogram findings of this patient. The liver and spleen neoplasm was observed stable, while the biliary sludge volume fluctuated. The treatment strategy recorded is Ondansetron, Samylin® (S-adenosil L-metionina (SAMe), silybin, vitamin E, and vitamin C), Ornipural and Ursodeoxycholic acid.

Keywords: Blood biochemistry profile; Hematology; Liver neoplasia; Ultrasonography

ABSTRAK

Neoplasia hati adalah replikasi hepatosit yang berlebihan dan tidak terkendali yang membentuk nodul yang dapat terlihat pada ultrasonografi. Penelitian ini bertujuan untuk mempelajari dan membahas karakteristik, diagnosis dan pengobatan neoplasma hati melalui interpretasi ultrasonografi dan hematologi pada anjing ras Shih Tzu. Ultrasonografi dilakukan dengan mesin ultrasonografi Chison Q8 dengan probe cembung frekuensi 5-7 MHz pada posisi rebah samping atau berbaring miring. Sel darah, enzim hati dan ukuran nodul

merupakan parameter utama dalam penelitian ini. Hasil dalam kurun waktu tiga tahun dari 2021-2023 ditafsirkan dan didukung dengan sumber data sekunder. Anjing Shih Tzu yang dijadikan kasus berusia 14 tahun pada tahun 2023 dengan bobot badan 5,21 kg. Tidak ada tanda-tanda klinis yang jelas yang diamati selama pemeriksaan sebelumnya. Namun, kelesuan, muntah dan anoreksia tercatat dalam pemeriksaan terakhirnya. Trombositosis, granulositosis, kadar enzim hati yang tinggi dan hipoglikemia merupakan beberapa manifestasi klinis neoplastik, juga ditunjukkan oleh pasien ini. Selain itu, neoplasma hati, neoplasma limpa dan lumpur empedu terlihat pada hasil sonogram pasien ini. Neoplasma hati dan limpa tampak stabil, sedangkan volume lumpur empedu berfluktuasi. Strategi pengobatan yang diberikan adalah Ondansetron, Samylin® (S-adenosil L-metionina (SAMe), silybin, vitamin E dan vitamin C), Ornipural dan asam ursodeoksikolat.

Kata-kata kunci: profil biokimia darah; hematologi; neoplasia hati; ultrasonografi

INTRODUCTION

The liver is one of the body organs that are susceptible to tumors. Its function in blood filtration, increases the risk of malignancy as a result of tumor cells metastasis to the liver via blood circulation (Kalra *et al.,* 2022). Liver neoplasm (tumor) is the abnormal and uncontrolled replication and proliferation of heaptocytes. Liver neoplasm in dogs can be morphologically categorized into three categories, namely massive, nodular and diffuse neoplasm (Liptak 2020). Neoplasm growth can be locally (focal) or it can spread throughout the liver (diffuse). Liver neoplasm may be benign or malignant. Malignant neoplasm can also be classified into primary and secondary (Fossum *et al.,* 2013).

Animals with liver neoplasm may show nausea, vomiting, weight loss, diarrhea, abdominal distension, lethargy or polydipsia and polyuria (Fossum *et al.,* 2013). The abnormalities of the liver can be diagnosed using abdominal ultrasound (USG) or computed tomography (CT). Ultrasound is preferable as it produces real-time imaging and is relatively safe, non-invasive and provides a definite anatomic and hemodynamic diagnosis (Noviana *et al.,* 2018). Furthermore, it also determines the changes in size, shapes and locations of liver masses. The supporting diagnostic tests that can be done are complete blood count, blood chemistry profile and urinalysis.

The treatment of liver neoplasm depends on the type and size of the tumor and the animal's condition (Liptak 2020). However, symptomatic treatment can be used to control the animal's condition, reduce clinical signs and support the health of the patient. The differentiation of types of liver neoplasms are challenging as it requires few supporting diagnostic tests. However, with ultrasonography, the early identification of liver neoplasm can be obtained. Hence, it increases the prognosis of the patient. The objective of this case study was to study and discuss the characteristic, diagnosis and treatment of liver neoplasm through the interpretation of ultrasonography and hematology in a Shih Tzu dog. This clinical case study is expected to provide a comprehensive overview of the clinical, laboratory and therapy approaches on liver neoplasm in the Shih Tzu dog as well as for ultrasonography and hematology examination references.

RESEARCH METHODS

This study was done under ultrasonography examination with a portable ultrasound machine (Chison Q8, Jiangsu, China), a convex probe with a frequency of 5 to 7 MHz and an automated hematology analyzer. Materials used are a 14-year-old female Shih Tzu dog, water-based acoustic gel, EDTA (Etilenadiamintetraasetat) vacutainers, plain vacutainers, Ondansetron, Orni-pural, Samylin® (S-adenosil L-metionina (SAMe), silybin, vitamin E, and vitamin C), and Ursodeoxycholic acid.

Hematology

Blood was collected from the cephalic vein. A 21 gauge needle was used to collect 2 to 5 mLof blood samples. The blood samples are then transferred into two vacutainers, namely the ethylenediaminetetraacetic acid (EDTA) purple vacutainer for the complete blood count (CBC) test and the plain vacutainer for blood biochemistry profile test.

Ultrasonography Examination

Hair clipping is done in the whole ventral abdomen. The patient is placed in a dorsal recumbency. A generous amount of acoustic gel is applied onto the examination area and spread evenly using the probe. Ultrasonography started with the liver examination by placing the probe on the midline at the xiphoid cartilage. All the abdominal organs will be examined. The changes in size, density and shape of the abdominal organs are recorded.

RESULTS AND DISCUSSION

Sign and Anamnesis

A female Shih Tzu dog visited Animal Teaching Hospital, School of Veterinary Medicine and Biomedical Sciences, IPB University,for its routine check-up on 13 December 2021, 22 March 2022, 16 August 2022 and 14 February 2023. The sign recorded was a 14-year-old female Shih Tzu dog with a body weight of 5.21 kg in latest checkup. There were no obvious clinical signs observed during its previous examination. However, lethargy, vomiting and anorexia were menti-oned by the client when it returned on 14 February 2023.

Lethargy, vomiting and anorexia are the few common nonspecific clinical manifesttations of neoplasms that can be observed in neoplastic diseases or be the result of gallbladder deposition (Lee *et al.,* 2018; Gulersoy *et al.,* 2021; Butler *et al.,* 2022). According to the previous abdominal ultrasound examination, multiple hyperplasia nodules were found in the liver and a single hyperplasia nodule was found in the spleen. Generally, the condition of the abdominal organs is still stable.

Interpretation of Complete Blood Count (CBC) and Blood Biochemistry Profile Report Complete blood count (CBC) results of the first and second hema-tological examinations data (Table 1) revealed that the leukocyte, thrombocyte and granulocyte counts were higher than the normal ranges. Furthermore, the erythrocyte count was slightly higher in the second examination. Erythrocytosis is defined as high circulating red blood cell count in blood circulation. Generally, it can be caused by dehydration, spleen contraction or bone marrow diseases (Randolph *et al.,* 2022). Thrombocytosis is defined as high platelet production. It is recognized as a paraneoplastic syndrome of liver neoplasm (Gibson *et al.,* 2022). According to research by Stone *et al.* (2012), tumor-derived interleukin-6 (IL-6) production is the key factor that leads to paraneoplastic thrombocytosis, where it increases the hepatic thrombopoietin synthesis, which in turns increases the platelet counts.

Leukocytosis, elevation of white blood cell count in blood may be correlated to the high granulocyte count. This is because granulocytes include neutrophils, eosinophils and basophils, while leukocytes consist of granulocytes, lymphocytes and monocytes (Sieminska *et al.,* 2021). However, since differential granulocyte count was not evaluated, hence the definite reason that led to granulocytosis was not determined. Nevertheless, as mentioned by Uribe-Querol and Rosales (2015), elevations of neutrophils can be presented in cancer patients, which explains the presence of high granulocytes count.

According to both blood biochemistry profiles (Table 2), alkaline phosphatase (ALP) and alanine transaminase (ALT) recorded were significantly greater than the normal range. The high ALP levels may indicate gallbladder disorder which can be observed in the gallbladder sonogram that showed mass deposition in its lumen. A high ALT indicates disrupted hepatocellular membrane leading to the leakage of liver enzymes. Aspartate amino-transferase (AST) and glucose levels were recorded low. As mentioned by Liptak (2020),

hypoglycemia is a paraneoplastic syndrome secondary to hepatic neoplasia. It occurs due to the insulin-like growth factor 2 (IGF-2) production by neoplastic liver tissue (Gibson *et al.,* 2022).

A high blood urea nitrogen (BUN) was recorded on 22 March 2022 (Table 2). It may be caused by dehydration or impaired renal function. Based on the ultrasonography examination, left kidney cyst and right kidney nephrolithiasis were observed. According to the research done by Vagias *et al.* (2022), most dogs with renal cysts did show an increase in BUN, ALP, ALT, creatinine and cholesterol levels. Creatinine is synthesized from the liver and it enters skeletal muscles. A decrease in creatinine level can be caused by damage to hepatocytes function or loss of muscle mass (Coyne *et al.,* 2020).

Interpretation of Ultrasonography Result

All four examinations of liver ultrasonography (Figure 1) showed inhomogeneous liver parenchymal texture and multiple hypoechoic nodules were observed. The presence of hypoechoic nodules disturbs the liver parenchymal homogeneity. The nodules measured have a constant diameter that ranged between 2.0-7.5; 2.6-6.5 and 1.5-6.5 mm in the left liver lobe (LLL), right liver lobe (RLL) and central liver lobe (CLL) (Figure 1) respectively in all four exa-minations of liver ultrasonography. No abnormalities were observed in both the portal and hepatic veins. The portal vein appeared in a smooth hyperechoic wall and the hepatic vein had a smooth and thin hypoechoic wall.

Differential diagnoses of hypoechoic nodules with ultrasonography include nodular hyperplasia, metastasis, lymphoma, primary liver neoplasia, abscess, necrosis, and etc. According to Penninck and d'Anjou (2015), multiple; less than 1 mm; hypoechoic focus are seen in the liver of a dog suffering from nodular hyperplasia which is similar to the multifocal nodules presented in Figure 1.

These differential diagnoses may have similar ultrasonography description and may be eliminated based on its clinical signs or sonogram differences if other further diagnostic methods are not available. The presence of shadowing or reverberation artifact facilitates the differentiation of foreign bodies, gas and minerals from neoplasms, abscess or hematomas as they do not produce such artifacts in a sonogram (Burk and Feeney, 2003). For instance, an abscessed region in the liver is poorly marginated and hyperechoic foci may be seen. Dogs with liver abscess may show fever and abdominal pain. Septic abscess is indicated by a poorly defined hyperechoic nodule with hypoechoic center in the liver (Penninck and d'Anjou, 2015). Presence of gasses in abscess can be further confirmed with radiography.

According to Penninck and d'Anjou (2015), lymphoma may involve the liver without the presence of any detectable ultrasonographic changes. Some may show diffuse hyperechogenicity, hypoechogenicity or mixed echogenicity with or without diffuse hepatomegaly and nodules. The nodules present in lymphoma are big, well-defined and hypoechoic. Dogs suf-fering from hepatic lymphoma may show leukocytosis, neutrophilia, hypoalbuminemia or hyperbilirubinemia (Dank *et al.,* 2011). Hepatic infarction may show an irregular hypoechoic region with peripheral vascular signal (Penninck and d'Anjou, 2015).

According to the anamnesis, the hyperplastic nodule in the spleen was found prior to the hyperplastic nodules in the liver in the abdominal sonogram. In accordance with the sequence of nodules found, the nodules developed in the liver can be assumed to be metastasized cells from the spleen. This assumption is made because the possibility of secondary malignant neoplasm is higher than primary neoplasms in the liver (Obradovich 2016). In the abdominal ultrasonography performed on 13 December 2021 (Figure 2a), a single mixed echogenicity hyperplasia

Table 1. Complete Blood Count (CBC) report

Parameters	Result 1 (13 December 2021)	Result 2 (22 March 2022)	Normal Velues in Dogs
Erythrocyte (RBC) (10^6/µL)	6.48	8.22	4.95 – 7.87 [α]
Thrombocyte (PLT) (10^3/µL)	506	565	150 – 400 [β]
Leukocyte (WBC) (10^3/µL)	16.4	14.9	5 – 14.1 [α]
Granulocyte (10^3/µL)	13.4	12.8	3.5 – 12 [γ]
Granulocyte (%)	81.8	85.7	43 – 80 [γ]

[α]Source: Latimer 2011, [β]Source: UCDAVIS 2011, [γ]Source: Grondahl 2019. RBC= Red Blood Cell, PLT= platelet, WBC= White Blood Cell.

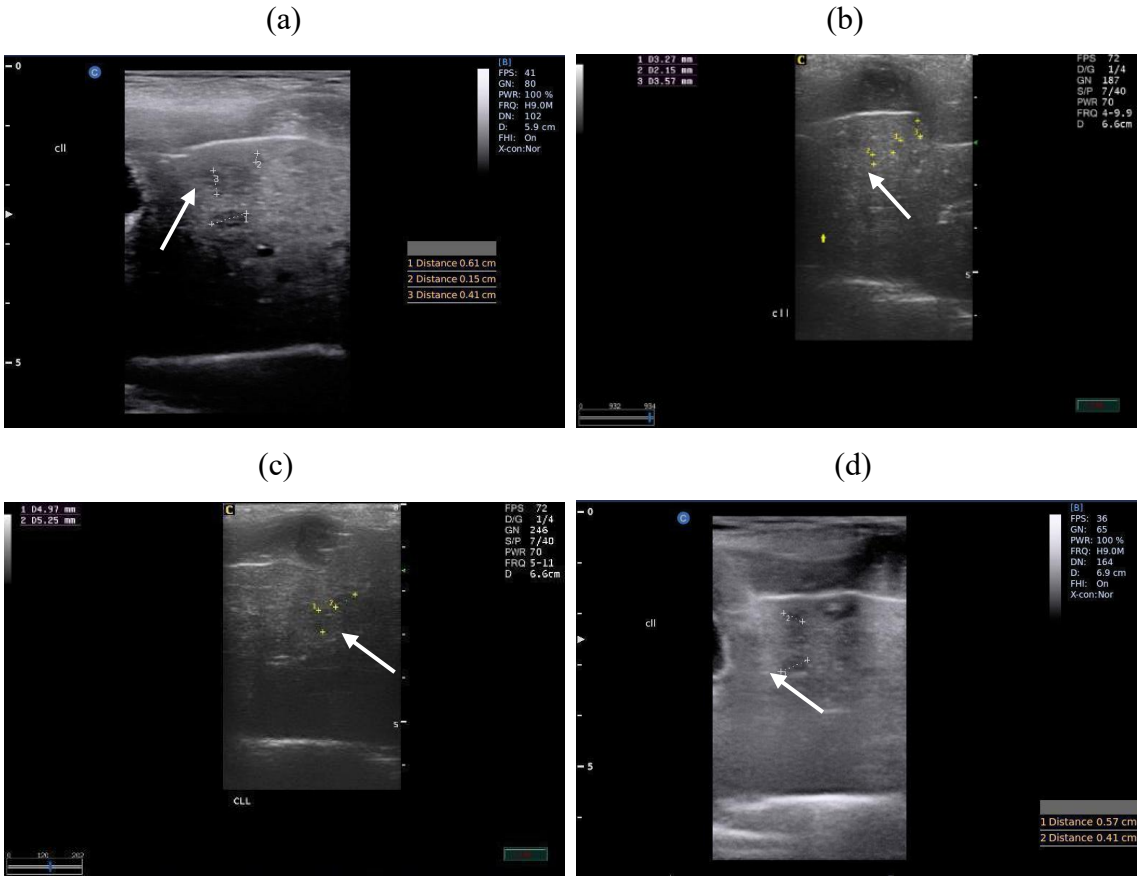

Figure 1. The Central liver lobe (CLL) parenchyma sonogram of Shih Tzu dog showing inhomogeneous texture with multiple various sizes of hypoechoic nodules. a= 13 December 2021, b= 22 March 2022, c= 16 August 2022, d=14 February 2023. Arrow: Hypoechoic nodules.

Figure 2. Spleen sonogram of Shih Tzu dog showing a single hyperplasia nodule with mixed echogenicity. a=13 December 2021 b= 22 March 2022, c= 16 August 2022, d= 14 February 2023. Arrow: spleen capsule. Star: mixed echogenicity nodule.

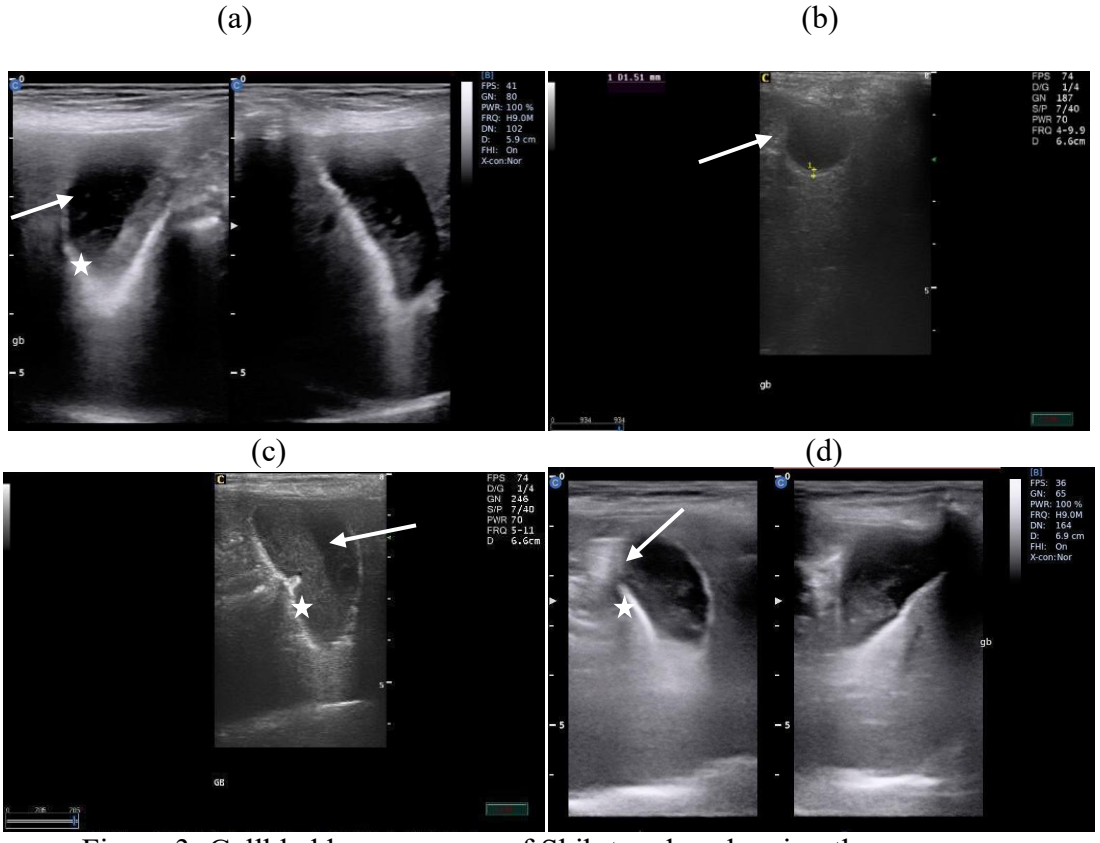

Figure 3. Gallbladder sonogram of Shih tzu dog showing the presence of deposition in the gallbladder lumen. a= 13 December 2021, b= 22 March 2022, c= 16 August 2022, d=14 February 2023. Arrow: bile. Star: biliary sludge.

Table 2. Blood chemistry profile report

Parameters	Result 1 (13 December 2021)	Result 2 (22 March 2022）	Normal Velues in Dogs*
Alkaline phosphatase (ALP) (IU/L)	700	> 1500	1 – 114
Alanine transaminase (ALT) (IU/L)	139	142	10 – 109
Aspartate aminotransferase (AST) (IU/L)	8	11	13 – 15
Glucose (mg/dL)	62	14	76 – 119
Ureum (BUN) (mg/dL)	13	109	8 – 28
Creatinine (mg/dL)	0.4	0.5	0.5 – 1.7

*Source: Latimer 2011. BUN=Blood Urea Nitrogen.

nodule with a diameter of 11.4 mm was observed in the spleen's body. However, the diameter decreased to an average of 8.1 to 8.9 mm in the following ultrasonography examinations (Figure 2b to d). This may be due to different scanning angles during ultrasonography. The mixed echogenicity nodule appears with a hyperechoic center and a hypoechoic rim that is induced respectively by tumor necrosis and the tumor itself, is called "target-like" lesions (Hecht and Mai, 2015). The thin hyperechoic layer with a regular margination surrounding the hypo-hyperechoic area in the sonogram (arrow) is the spleen capsule. No abnormalities were observed in the head (cranial) and tail (caudal) of the spleen.

All four gallbladder sonograms (Figure 3) showed the presence of anechoic fluid and hypoechoic deposition in the gallbladder lumen. The anechoic fluid represents the bile, while the hypoechoic fluid is the biliary sludge. The gallbladder wall observed had a smooth and thick hyperechoic wall on 13 December 2021 (Figure 3a) and around 20% of deposition was found. After treatment with 10 mg/kg Ursodeoxycholic acid once daily, made the the biliary sludge decreases. This is evident in the sonogram on 22 March 2022 (Figure 3b) where the deposition reduced to 5% and the gallbladder wall is in the normal range (1.51 mm). Unfortunately, on 16 August 2022, the deposition increased to 50% indicating recurrence of biliary sludge formation and the gallbladder wall thickens (Figure 3c). Therefore, the dosage of Ursodeoxycholic acid 10 mg/kg was increased to twice daily. After the change in therapy, the biliary sludge in the gallbladder lumen decreases to 30% (Figure 3d). The gallbladder wall remains thick and uneven.

Biliary sludge is a common asymptomatic incidental finding in healthy dogs (Saunders *et al.,* 2017). In a sonogram, biliary sludge appears as low-amplitude homogeneous echoes that cause the formation of acoustic enhancement below it (Secchi *et al.,* 2012). The formation of biliary sludge is associated with gallbladder dysmotility, bile congestion and mucin hypersecretion. The mucin will mix with cholesterol and calcium salts and form sludge if they are present in the gallbladder lumen for a long time (Saunders *et al.,* 2017).

Medications that were given to the patient includes a weekly 0.1-0.2 mg/kg Ondansetron injection intramuscularly (IM), a weekly 2 to 5 mL/kg Ornipural injection subcutaneously (SC), one Samylin® tablet once daily before meal and 10-15 mg/kg Ursodeoxycholic acid twice a day after meal (Papich 2016; MUM 2023; Plumb 2011). Ondansetron is a potent anti-emetic drug, indicated to prevent nausea and vomiting induced by chemotherapy, radiation and surgery (Hesketh *et al.,* 2017). Ornipural contains hepatoprotective active

ingredients that activate the liver function by main-taining normal physiological processes, heaptocytes regeneration and reducing apoptosis (El Okle *et al.,* 2022). Samylin® contains S-adenosyl L-methionine (SAMe), silybin and vitamin E which are hepato-protective. They protect hepatocytes from bile salt damage (Allerton *et al.,* 2020). Besides, the use of Ursodeoxycholic acid (ursodiol) also reduces hepatocellular injury by improving biliary circulation (Plumb 2011). It possesses hepatoprotective effects through its anti-oxidative properties (Saun-ders *et al.,* 2017). It is also given to stop vomiting caused by biliary sludge by relieving the problems in the gallbladder.

In this study, the Shih Tzu dog suffered from liver neoplasm, spleen neoplasm and biliary sludge. The multiple hypoechoic nodules observed in the abdo-minal ultrasonography indicate the presence of liver neoplasm. Hematology test that reveals thrombocytosis, granulocytosis, ele-vated liver enzymes and hypoglycemia strengthening the diagnosis of liver neoplasm. A single mix echogenicity nodule in the spleen sonogram indicating spleen neoplasm, was the first neoplastic nodule observed. The hypoechoic deposition in the gallbladder sonogram was the incidental finding of this case study. Ondansetron, Ornipural, Samy-lin® and Ursodeoxycholic acid were given to control the liver neoplasm and biliary sludge condition. Overall, based on hematology and ultrasonography examination, the condition of the patient was considered stable.

CONCLUSION

In conclusion, the Shih Tzu dog in this case was diagnosed with liver neoplasm (hypoechoic nodule, thrombocytosis, granu-locytosis, elevated liver enzymes, hypo-glycemia), splenic neoplasm (echogenic nodule, and biliary sludge (hypoechoic deposition). Ondansetron, Ornipural, Samy-lin®, and ursodeoxycholic acid were admi-nistered successfully to control the liver neoplasm and biliary sludge conditions, and the patient's condition was stable after therapy.

SUGGESTION

Fine needle aspiration (FNA) can be studied to differentiate neolpastic cells in order to be used as a beneficial alternative in identifying the types of neoplasms. Contrast-Enchanced Ultrasonography can also be studied to identify the contrast pattern for each specific types of neoplasms.

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