

## Cardiac Lymphoma in a Shih Tzu Dog

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**Abstract :** A 7 years-old intact female dog (4.8 kg) was referred with primary complaints of enlarged surface lymph nodes, cardiac murmur, coughing and exercise intolerance. Diagnostic imaging studies found cardiomegaly with distended caudal vena cava, marked left ventricular and interventricular septal thickening and flattening, severe aortic and pulmonic stenosis (~5 m/s), and mitral and tricuspid regurgitation (~4 m/s). Cytology for the samples obtained from submandibular lymph node and left ventricle revealed high grade malignant lymphoma. The case was diagnosed as cardiac lymphoma. The dog was treated with prednisolone (2 mg/kg, PO, q24h), lomustine (80 mg/m<sup>2</sup> PO, q3wk), diltiazem (1 mg/kg, PO, q12h) and enalapril (0.5 mg/kg, PO, q12h). The clinical signs were improved after therapy. The dog is still on the chemotherapy and regularly checked up.

**Key words :** lymphoma, cardiac tumor, pulmonic stenosis, aortic stenosis, heart.

### Introduction

Canine lymphoma is a fatal disease characterized by the malignant clonal expansion of lymphoid cells at lymphoid tissues (e.g., bone marrow, thymus, lymph nodes, and spleen) and extranodal sites (e.g., skin, eye, CNS, testis, bone and heart). Cardiac lymphoma has been reported in dogs, although all cardiac tumors in dogs are uncommon (18). One large survey of cardiac tumors in dogs found the hemangiosarcoma took up to 46% of all tumor, while aortic body tumors and lymphoma took up 5% and 2%, respectively. In human, the primary cardiac lymphoma is often associated with human immunodeficiency virus and other causes of severe immunosuppression (6,16,18). However, no study found a viral association in dogs with lymphoma, although some immunosuppressive disorders can worsen the clinical manifestations of lymphoma in dogs. Generally cardiac lymphoma in humans progresses rapidly and has poor prognosis (6). Similarly, the prognosis of cardiac lymphoma in dogs is poor (10,16). This case study describes the rare case of lymphoma involves in body surface lymphoid tissues and myocardium in a Shih Tzu dog.

### Case

A 7 years-old intact female dog (4.8 kg) was referred with primary complaints of enlarged surface lymph nodes, cardiac murmur, coughing and exercise intolerance. At presentation,

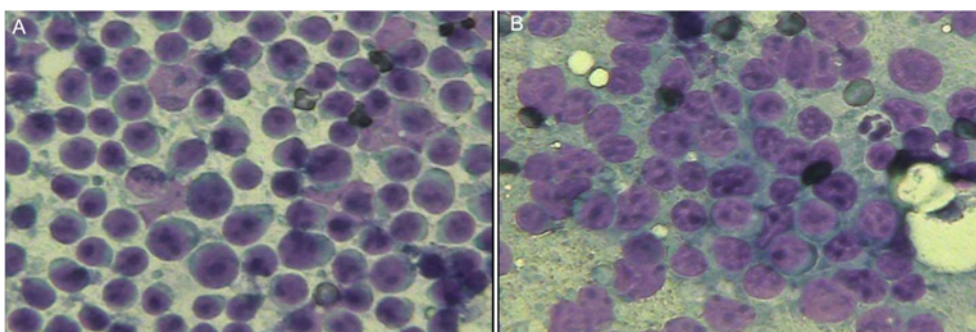
the dog was depressed, anorexia and anemic. On palpation, submandibular, superficial and deep cervical, cranial mediastinal, axillary, accessory axillary, superficial inguinal and popliteal lymph nodes were enlargement. The systolic pressure was ~140 mmHg (measured by Doppler method) and body temperature (38°C). The dog had grade 4/6 moderate systolic murmur at left base of heart. On ECG, the heart rhythm was predominantly normal sinus rhythm but R wave amplitudes are various.

CBC and serum biochemistry results were unremarkable except for slight decrease to lower limit in blood cells. Laboratory tests revealed normal leukocyte count ( $6.28 \times 10^3/\mu\text{L}$ , reference range  $6-17 \times 10^3/\mu\text{L}$ ) which is nearly lower limit, mild anemia ( $5.62 \times 10^{12}/\mu\text{L}$ , reference range  $5.5-8.5 \times 10^{12}/\mu\text{L}$ ) with slightly decreased hematocrit (31.3%, reference range 37-55) and mild thrombocytopenia ( $168 \times 10^3/\mu\text{L}$ , reference range  $200-500 \times 10^3/\mu\text{L}$ ).

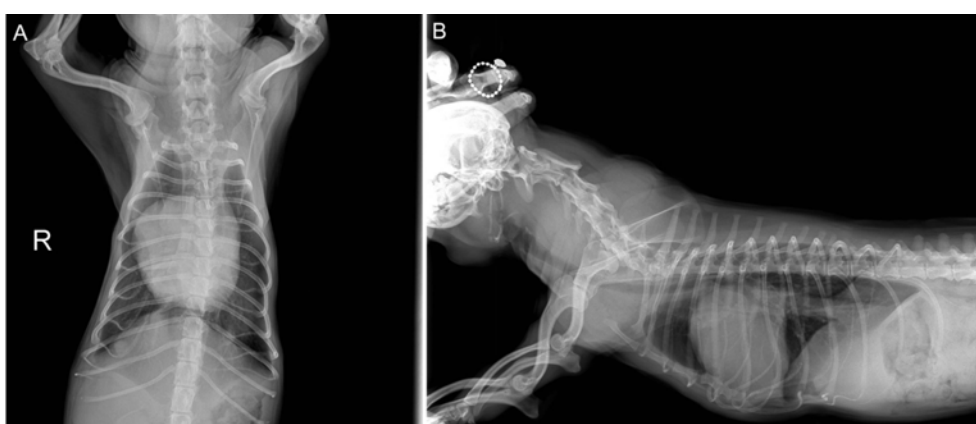
Cytology of this case obtained from submandibular lymph node (Fig 1A) and left ventricle of heart (Fig 1B). Immature lymphocytes were predominant (> 80%), indicating the malignancy of this case.

Ventrodorsal view of thoracic radiography showed reversed D shaped cardiac shadow with enlargement of right ventricle and main pulmonary artery (Fig 2A) and lateral view showed increased sternal contact of cardiac shadow, elevation of trachea, right and left atrial enlargement, increased soft tissue density at cardiac base (Fig 2B). The caudal vena cava was also enlarged in both views of thoracic radiography. Those findings strongly suggested both-sided heart failure. On echocardiography, the left (LV) and right ventricles (RV) were remarkably thickened (Fig 3A). The thickness of LV

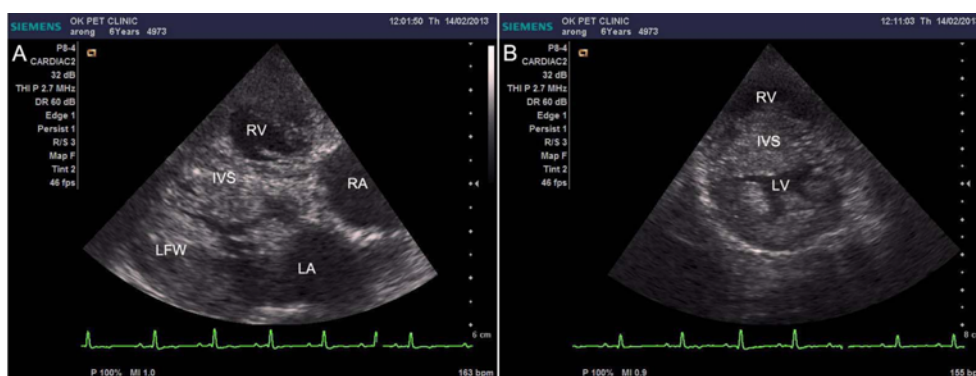
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**Fig 1.** Cytology of this case obtained from submandibular lymph node (A) and left ventricle of heart (B). Diff-Quik stain, 1000 ×. Immature lymphocytes were predominant (> 80%), indicating the malignancy of this case.



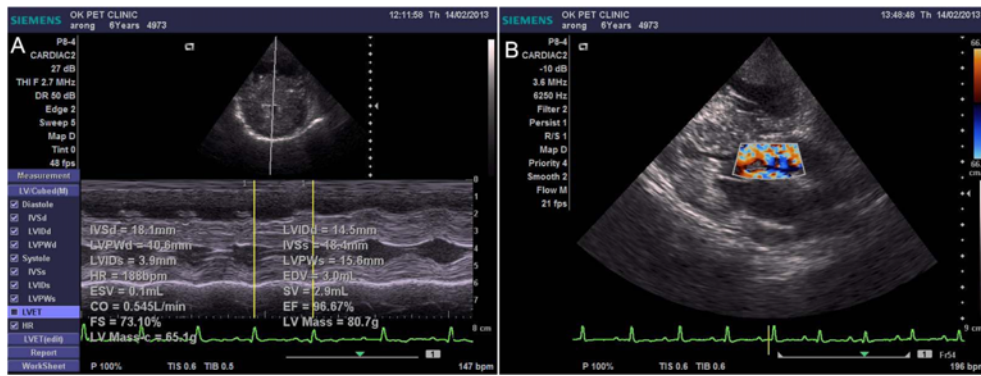
**Fig 2.** Thoracic radiography of this dog. A: Ventrodorsal view of thoracic radiography showed reversed D shaped cardiac shadow with enlargement of right ventricle and main pulmonary artery. B: Lateral view of thoracic radiography showed elevation of trachea, right atrial enlargement, increased soft tissue density at cardiac base. The caudal vena cava was also enlarged in both views of thoracic radiography.



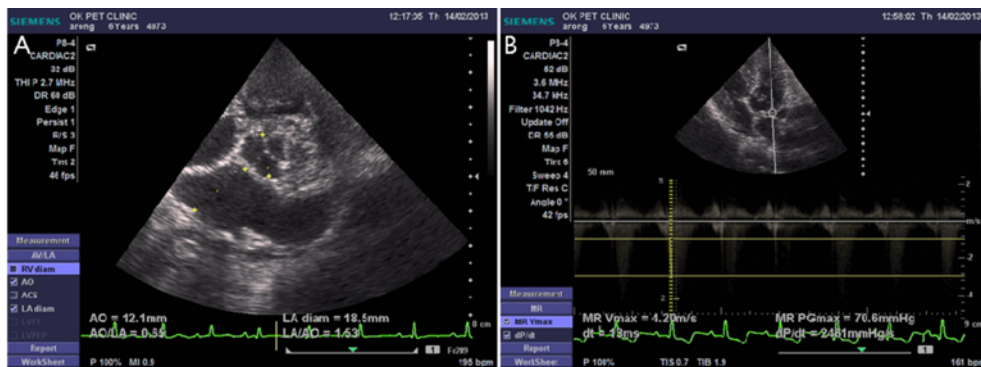
**Fig 3.** Echocardiography of this dog. A: The 2D-echocardiography of the right parasternal long axis of 4 chamber view showed the left ventricle (LV) and interventricular septum (IVS) were remarkably thickened. B: The M-mode echocardiography of the right parasternal short axis of left ventricle (papillary level) showed relative narrowing of left ventricular inner dimension and septal flattening. The echogenicity of LV free wall and IVS were heterogeneous and markedly thickened. RV: right ventricle, LA: left atrium, RA: right atrium.

free wall at diastole (LVFWd) and systole (LVFWs) and inter-ventricular septal wall at diastole (IVSd) and systole (IVSs) were 10.6 mm, 15.6 mm, 18.1 mm and 18.6 mm, respectively. Due to both ventricular hypertrophy, there were relative narrowing of left ventricular inner dimension and septal

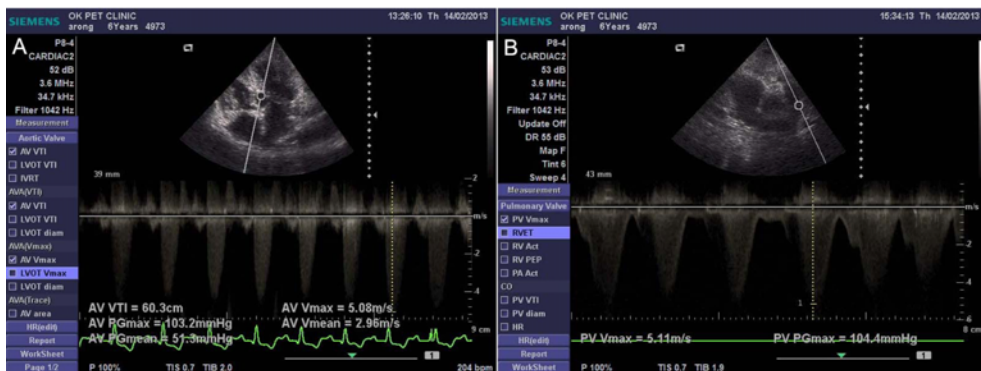
flattening (Fig 3B). Therefore, the % fractional shortening (FS) and %left ventricular ejection fraction (LVEF) were remarkably increased (%FS: 73%, %LVEF: 97%; Fig 4A). The left atrial-aortic diameter ratio (LA:Ao) was 1.53:1, indicating mild left atrial dilation (Fig 5A). In addition, there



**Fig 4.** Echocardiography of this dog. A: The M-mode echocardiography of the right parasternal short axis of left ventricle (papillary level) showed the LV free wall and IVS were markedly thickened. The % fractional shortening (FS) and %left ventricular ejection fraction (LVEF) were remarkably increased (%FS: 73%, %LVEF: 97%). B: Color Doppler echocardiography showed the mosaic systolic jet at the left ventricular outflow tract indicating aortic stenosis.



**Fig 5.** Echocardiography of this dog. A: Echocardiography of the right parasternal short axis of aortic level showed the left atrial-aortic diameter ratio (LA:Ao) was 1.53:1, indicating mild left atrial dilation. B: Continuous wave spectral Doppler study at mitral valve, apical view revealed moderate mitral regurgitation (peak velocity 4.2 m/s, pressure gradient 70.6 mmHg).



**Fig 6.** Echocardiography of this dog. A: Continuous wave spectral Doppler study at aortic valve revealed severe aortic systolic jet (peak velocity 5.08 m/s, pressure gradient 103.2 mmHg). B: Continuous wave spectral Doppler study at pulmonic valve revealed severe pulmonary systolic jet (peak velocity 5.11 m/s, pressure gradient 104.4 mmHg).

were moderate mitral regurgitation (peak velocity 4.2 m/s, pressure gradient 70.6 mmHg; Fig 5B) and tricuspid regurgitation (peak velocity 3.9 m/s, pressure gradient 60 mmHg), severe aortic stenosis (peak velocity 5.08 m/s, pressure gradient 103.2 mmHg; Fig 6A) and pulmonary stenosis (peak

velocity 5.11 m/s, pressure gradient 104.4 mmHg; Fig 6B). Color Doppler echocardiography showed the mosaic systolic jet at the left ventricular outflow tract (LVOT) indicating aortic stenosis (Fig 4B). There were no changes of echogenicity in other vital organs (e.g., liver, spleen, kidney). Based on

diagnostic studies, the case was diagnosed as cardiac lymphoma with ISACHC II heart failure.

The initial therapeutic goals for this case were 1) to lessen cardiac lymphoma with chemotherapy (prednisolone 2 mg/kg, PO, q24h, and lomustine 80 mg/m<sup>2</sup> PO, q3wk) 2) to improve the left ventricular relaxation (diastolic filling) using calcium channel blocker (diltiazem SR, 1 mg/kg, q12h, PO, Handok, Korea), and 3) to prevent neurohormonal activation (enalapril, 0.5 mg/kg, q12h, PO; Merial, USA). After 1 wk of therapy, the condition of dog was much stabilized and thus released with prescription of prednisolone (2 mg/kg, q24h, PO), diltiazem SR (1 mg/kg, q12h, PO) and enalapril (0.5 mg/kg, q12h, PO). At the presentation, the dog was more active and alert. The size of surface lymph nodes was dramatically reduced. However, leukopenia ( $2.9 \times 10^3/\mu\text{L}$ , reference range  $6-17 \times 10^3/\mu\text{L}$ ) with neutropenia ( $1.5 \times 10^3/\mu\text{L}$ , reference range  $4-10 \times 10^3/\mu\text{L}$ ) was noticed on the hemogram. Therefore, a broad spectrum antibiotic agent (cephalexin, 20 mg/kg, q12h, PO) was administered to prevent the secondary infection. The echocardiography also found dramatically improved left ventricular relaxation. The thickness of LVFWd, LVFWs, IVSd and IVSs were 8.6 mm, 10.6 mm, 12.3 mm and 14.3 mm, respectively, suggesting remarkable reduction of cardiac wall thickness. Despite remarkable cardiac improvement, the systolic jets at LVOF and RVOF were persisted. The dog is still on the chemotherapy and regularly checked up.

## Discussion

Cardiac tumors including lymphoma are rare in both animals and humans (4,8). One retrospective study found that prevalence of cardiac tumors was 0.19% of all tumors in dogs. Although hemangiosarcoma was occurring 10 times more frequently than any other cardiac tumors, cardiac lymphoma has sometimes occurred in dogs. Although cardiac tumors can be occurred primarily and secondarily, the true proportion of primary cardiac tumors has yet been defined (18). Cardiac metastases of malignant lymphoma and mammary carcinoma were seen most frequently (2). In dogs, cardiac metastases were seen mainly in the LV free wall. This is in contrast to the findings in man, in which about 30% were found in the RV free wall, 30% in the LV free wall, and 30% in both free walls (13). In this case, the thickness of LV and IVS wall were remarkably increased, as noticed in other report (13). Furthermore, cytological examination on the surface lymph nodes found immature lymphocytes were predominant (> 80%), suggesting cardiac lymphoma might be due to the metastasis of surface lymph nodes.

Most cases of cardiac lymphoma are solid, infiltrative nodular tumors in 1 or multiple chambers of the heart (3,7,12). Massive infiltration of lymphoma cells in the myocardium results in irregular thickening of the walls of the heart, mimicking classic hypertrophic cardiomyopathy (9). Hypertrophy of the ventricular septum, without dilation of the heart chambers, results in the characteristic hemodynamic distur-

bances (9). The echocardiography of this case also found marked biventricular hypertrophy with mild mitral and tricuspid regurgitation made us suspect hypertrophic cardiomyopathy (HCM), although the primary HCM is rare in dogs. Furthermore, the echogenicity of LV free and IVS walls were heterogeneous, suggesting cellular infiltration. Unlike primary HCM, there was no distinctive left atrial (LA) dilation in this dog. Authors believed there might be not enough time to LA dilation due to rapid infiltration of lymphoid cells at the myocardium.

Clinical signs of cardiac lymphoma generally result from hemodynamic consequences (i.e., restricted ventricular filling, venous congestion and poor cardiac output). Arrhythmias also can contribute to hemodynamic compromise (1,5,15). However, in this case, there were no marked signs related to hemodynamic compromise, although the echocardiography found marked restrictive filling disturbances, as usually seen in severe HCM cats. One explanation for this finding is that hemodynamic changes might be not severe enough to cause heart failure, because the propagation of lymphoid cells to the myocardium was too rapid in this dog.

Lymphoma in dogs is very responsive to chemotherapeutic intervention. Many drugs have been used successfully in combination to treat lymphoma in dogs. The drugs most often used in first-line combinations include prednisolone, vincristine, cyclophosphamide, doxorubicin, and L-asparaginase. Other with a putative role include chlorambucil, methotrexate, vinblastine, lomustine (CCNU), actinomycin D, mitoxantrone, mechlorethamine, procabazine, cisplatin, and cytosine arabinoside (11,17). Although multidrug protocols are better than single-agent therapy, we used single-agent therapy with CCNU, because of the risk of toxic cardiomyopathy from some anti-cancer drugs. Concurrent treatment with CCNU and prednisone was well tolerated in dogs with multicentric lymphoma (14). Therefore we used this protocol for this case and found to be very effective at this moment. The size of surface lymph node decreased to 30% of the original lymph node by the one dose of CCNU. Although severe myeloid suppression was also noticed in this case after the first week of therapy, the leukogram was returned to normal range within 3 weeks of medication. Therefore we are administering this CCNU every 3 weeks with tapering dose of prednisolone. The dog is well tolerated for this chemotherapy and there are no signs for heart failure at this moment.

In summary, this case study describes the rare case of lymphoma involves in body surface lymphoid tissues and the myocardium in a Shih Tzu dog.

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## 씨츄 개에서 발생한 심장 림프종

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**요 약** : 7년령의 암컷 개(4.8 kg)가 표층 림프절 종대, 심잡음, 그리고 운동 불내성을 주증으로 의뢰되었다. 영상진단 학상에 후대정맥의 확장, 좌심실벽과 심실 중격의 현저한 비후와 편평화, 심한 대동맥과 폐동맥 협착(~5 m/s), 그리고 이첨판과 삼첨판의 역류(~4 m/s)가 관찰되었다. 하악림프절과 좌심실로부터 취득한 샘플에 대한 세포학적 분석에서 높은 단계의 악성 림프종이 나타났다. 이 증례는 심장 림프종으로 진단되었다. 환자는 prednisolone (2 mg/kg, PO, q24h), lomustine (80 mg/m<sup>2</sup> PO, q3wk), diltiazem (1 mg/kg, PO, q12h) 그리고 enalapril (0.5 mg/kg, PO, q12h)으로 치료 되었다. 임상증상은 치료 후에 개선되었다. 현재 환자는 여전히 화학요법을 실시하고 있으며, 주기적으로 상태를 확인 중이다.

**주요어** : 림프종, 심장종양, 폐동맥 협착증, 대동맥 협착증, 심장