Case Report

Naturally Occurring Peripheral T-cell Lymphoma Not Otherwise Specified (PTCL-NOS) with Systemic Dissemination in a Beagle

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Abstract

A 6-year-old intact female Beagle dog presented with acute vomiting. Abdominal ultrasound showed abdominal lymphadenopathy, ascites and a hyperechoic mass within the pancreas. Thoracic radiographs and echocardiography revealed cardiomegaly with pericardial effusion. The dog died following rapid deterioration and a subsequent necropsy revealed a multilobulated white-to-tan mass within the pancreas, attaching to the omentum, stomach and left adrenal gland. The heart was enlarged and infiltrated by similar coalescing off-white irregular masses. Histologically, the masses consisted of infiltrative sheets of large T lymphocytes replacing the normal architecture of the heart along with the lymph nodes, pancreas, stomach, omentum, left adrenal gland, right ovary, heart, liver, gall bladder as well as the lungs and eyes. Based on histomorphology and immunophenotyping, this case was diagnosed as peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) with systemic dissemination to unusual sites including the heart.

Keywords: multicentric lymphoma, canine T-cell lymphoma, visceral dissemination, canine neoplasm

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Introduction

Canine lymphoma (CL) is one of the most common tumours comprising 7-24% of all neoplasms in dogs (Kaiser, 1981). CL develops from clonal expansion of immature to mature B or T lymphocytes in lymphoid tissues but it can arise from almost anywhere in the body. The most common clinical presentations of CL are multicentric (80%), gastrointestinal (GI) (5-7%), mediastinal (5%) and cutaneous (3-8%) while extranodal involvement, particularly to the heart, is rare (Fontaine *et al*., 2009; Madewell *et al*., 1987; Ware and Hopper, 1999). CL is diagnosed by cytologic or histopathologic examination of the affected lymph nodes or extranodal sites and is differentiated into T-, B- lineage or atypical phenotype (NK cells) using a combination of cellular morphology and immunophenotyping (Harris *et al*., 1994; Valli *et al*., 2011; Valli *et al*., 2017). T-cell lymphoma is further classified into two categories including its precursor (T-cell lymphoblastic lymphoma/leukemia) and the mature cells (T-zone lymphoma, enteropathy associated T-cell lymphoma, cutaneous T-cell lymphoma and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)) based on the Revised European–American Lymphoma (REAL) classification of lymphoid neoplasms adopted by the World Health Organization (WHO) (Harris *et al*., 1994; Valli *et al*., 2011). Histologically, PTCL-NOS exhibits a diffuse proliferative pattern of large neoplastic T lymphocytes with prominent nucleoli and has high mitotic rate (Seelig *et* al., 2016; Valli *et al*., 2011). Compared with high-grade B- and T-cell lymphoma, PTCL-NOS is more aggressive and usually has anti-neoplastic drug resistant mechanisms (Frantz *et al*., 2012; Valli *et al*., 2013). Dogs with PTCL-NOS often present with generalised lymphadenopathy, while extranodal involvement is uncommon (Fournel-Fleury *et al*., 2002). As there are few cases of confirmed PTCL-NOS with cardiac involvement, this report presents a case of PTCL-NOS in a dog with systemic dissemination to atypical metastatic sites including the heart.

Clinical description

A 6-year-old, 15.5-kg, intact female Beagle dog was referred to Prasu-Arthorn Veterinary Hospital, Faculty of Veterinary Science at Mahidol University with acute uncontrolled vomiting. Physical examination revealed icteric oral and scleral mucosal membranes with abdominal discomfort in the cranial quadrant. Serum biochemistry revealed hypertransaminasaemia, hyperbilirubinaemia, raised canine pancreatic lipase immunoreactivity and hypoalbuminaemia. Other biochemical test results were within normal range. Complete blood count revealed anemia with 24% packed cell volume (reference range 35 - 45%). Abdominal ultrasonography revealed abdominal effusion with portal, splenic and gastric lymph node enlargement and a 1.9 x 2 cm hyperechoic mass with a hypoechoic centre in the pancreas. Thoracic radiographs revealed cardiomegaly (13 vertebral heart scale (VHS); reference range 8.7 - 10.7) (Buchanan and Bücheler, 1995). Echocardiography showed cardiomegaly with right ventricular wall thickening and mild pericardial effusion. Initial treatment included 4 mcg/kg/hr constant rate infusion (CRI) of IV fentanyl citrate (Fentanyl-hameln; Hameln pharma GmbH), 5% dextrose with acetate Ringer's solution at 4 ml/kg/hr (Glucose; A.N.B. Laboratories Co., Ltd.). One mg/kg IV ondansetron (Onsia®; Siam Bheasach Co., Ltd.) was given 12-hourly to control the vomiting. Twenty mg/kg IV Amoxicillin trihydrate/ clavulanate potassium (Cavumox®; Siam Bheasach Co., Ltd.) was given 12-hourly as empirical therapy as leptospirosis was a differential diagnosis. During hospitalisation, the dog became dyspnoeic and oliguric (urinary output 0.83 ml/kg/hr). Therefore, 0.5mg/kg IV Furosemide (H-Mide®; L.B.S Laboratory Ltd.) was administered 12-hourly in order to improve the respiratory distress but the dog died 12 hours after treatment.

A complete necropsy was performed at the Veterinary Diagnostic Centre, Faculty of Veterinary Science, Mahidol University. At necropsy, the oral and scleral mucosae were icteric and there was generalised lymphadenopathy involving the right axillary, tracheobronchial and mediastinal lymph nodes. The abdomen contained 29 ml of serosanguineous fluid and a 3 x 4 x 3.5 cm multilobulated pale-tan to yellow mass with ecchymoses within the left pancreatic lobe attaching to the omentum, gastric pylorus and fundus and the left adrenal gland (Figure 1). The cut surface of the mass revealed an homogenous pale-tan surface with area of haemorrhage. The gall bladder and gastric wall were markedly thickened. The right ovary was larger (measured 4 x 5 cm in diameter) than the left ovary (measured 3 x 3 cm in diameter). The pericardial sac contained 77 ml of serosanguineous fluid and the heart was markedly enlarged with multifocal coalescing firm, round to irregular, pale-tan to yellow areas varying between 5 mm to 2 cm in diameter within both ventricular walls (Figure 2A and B).

Representative specimens of all internal organ viscera were fixed in formalin fixative, processed and embedded into paraffin blocks before being cut into 5 µm thick sections that were stained with routine Hematoxylin and Eosin. All histopathologic slides were examined under a light microscopic scope. Microscopically, there were solid sheets of infiltrative proliferation of poorly delineated neoplastic large lymphocytes obliterating the normal architecture of multiple organs including the aforementioned lymph nodes, bone marrow, right ovary, pancreas, left adrenal gland, gastric wall, lungs, gall bladder, hepatic central veins and uveal tracts of both eyes. Neoplastic cells were round, contained scant pale eosinophilic cytoplasm with indistinct borders and had a high nuclear to cytoplasmic ratio. Nuclei were large (>2X RBC), finely stippled to vesiculate nuclei occasionally with multiple nucleoli. Anisokaryosis was moderate. There were 33 mitoses in 10 high-power fields. For the heart, similar neoplastic cells widely obliterated the architecture of the right and left atrium, extending to adjacent epicardial adipose tissue while multifocally infiltrated and dissecting around cardiac myofibres (Figure 3A and B). Such infiltrates of neoplastic cells also invaded the epineurium, perineurium and endoneurium and Purkinje's cells. For immunophenotyping, the heart specimen was submitted to the Veterinary Diagnostic Laboratory, Michigan State University. Immunohistochemistry

using polyclonal rabbit antibody against CD3 (Dako cytomation, 1:200) and polyclonal rabbit antibody against CD20 (Thermo Fisher, 1:200) was performed on a Bond-Max Automated System (Leica Microsystems) and Bond Polymer Detection System (Vision BioSystems: Leica) with 3,3′-diaminobenzidine (DAB) as the chromogen. The neoplastic cells exhibited perimembranous labeling for CD3 (Figure 4A and B) and were not immunoreactive for CD20 labeling (Figure 4C and D). Lymphoma subtype classification was performed based on the REAL and WHO classification systems using anatomic, morphologic and immunophenotypic criteria, PTCL-NOS was diagnosed in this case.

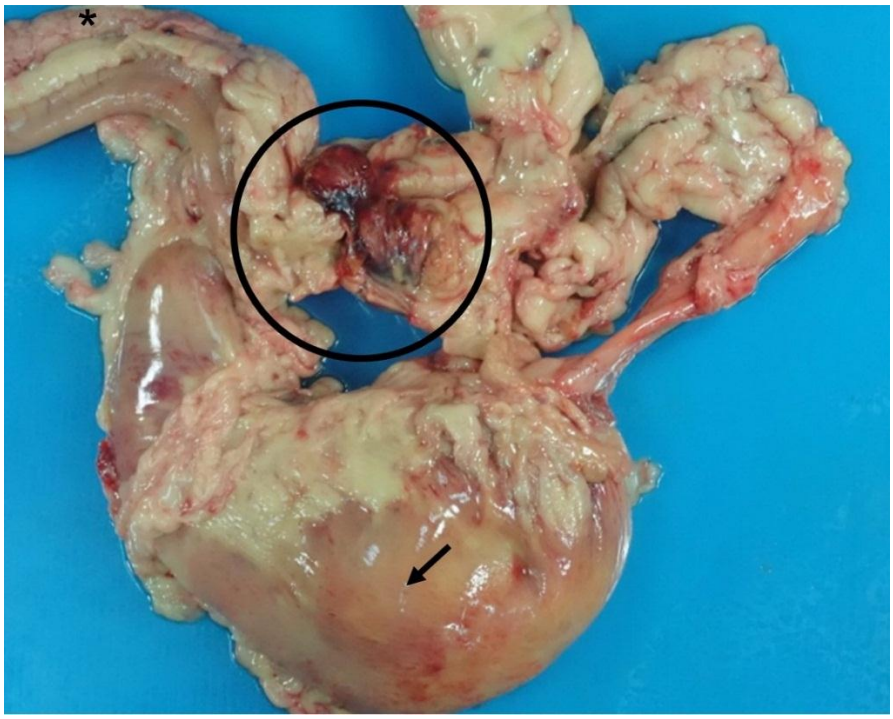

Figure 1 Abdominal mass. A 3 × 4 × 3.5 cm multilobulated nodular mass extending from the left pancreatic lobe (asterisk) and firmly attached to the stomach, omentum and left adrenal gland (circle). Multiple nodular masses are seen infiltrating the gastric wall (arrow)

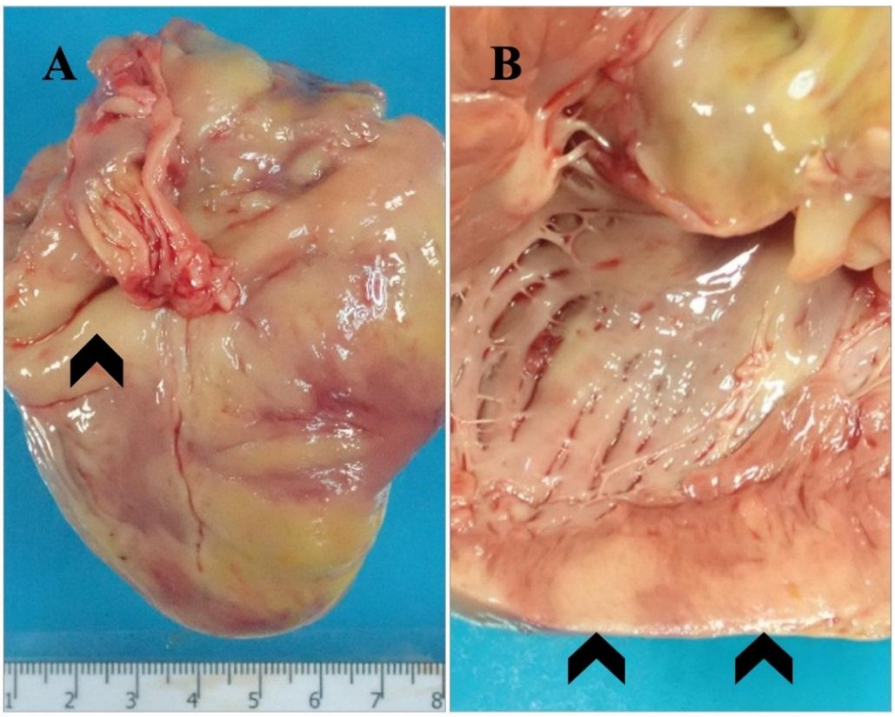

Figure 2 Heart. A) Variably sized areas of pale-tan to yellow discolouration and homogenous nodules scattered throughout the heart with multifocal and coalescing white nodular masses noted on the right atrium (arrowhead). B) Poorly demarcated areas of intramural infiltration involving the left ventricular wall (arrowheads).

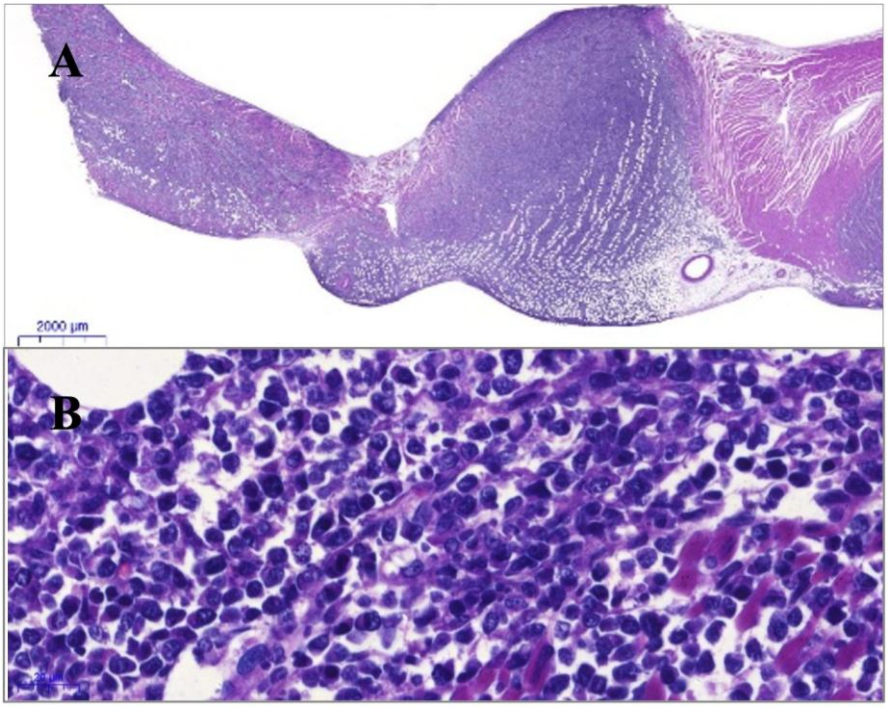

Figure 3 Heart. A) Sheets of monomorphic neoplastic cell infiltrates are seen effacing and replacing cardiac myofibres and the epicardial adipose tissue by. HE. Bar, 2000 µm. B) Neoplastic lymphocytes are large (1.75-2 × RBC) dissecting cardiac myofibrils and adjacent adipocytes. HE. Bar, 20 µm.

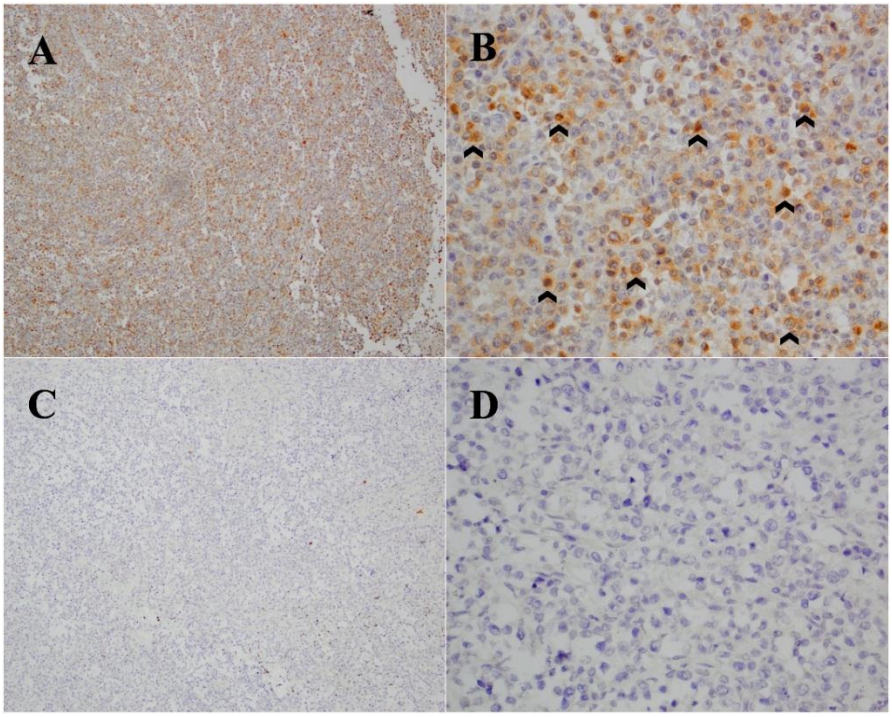

Figure 4 Immunophenotyping of the heart for surface markers. A) CD3 positive labelling is seen throughout the slide. 10.0 × magnification. B) Neoplastic cells are large (>1.75-2 × RBC) with variable cellular morphology containing prominent nucleoli, and exhibit perimembranous labeling for CD3. IHC. 40.0 × magnification (arrowheads). C) Rare to absent surface labelling for CD20. 10.0 × magnification. D) None of the neoplastic cells are immunoreactive for CD20. IHC. 40.0 × magnification.

Discussion

Although CL is common, the clinical presentations are non-specific and variable depending on the affected systems. Typically, dogs with multicentric CL present with generalised or localised lymphadenopathy (82.40%) while extranodal involvement occurs in 17.6% , particularly to the skin (12.34%), GI (1.48%), spleen (1.80%), tonsils (1.48%) and eyes (0.33%) (Ponce *et al*., 2010). In this case, the most remarkable clinical presentations were simultaneous cardiomyopathy with pericardial

effusion accompanied by pancreatitis, hepatomegaly and ascites. During the necropsy, generalised infiltrative disease was observed in several organs including the lymph nodes, pancreas, stomach, omentum, left adrenal gland, right ovary, heart, liver, gall bladder as well as the lungs and eyes. The involvement of the heart is unusual as the incidence of cardiac tumour is 0.19% of all neoplasms, of which the majority are primary cardiac tumour and only 16% are metastatic tumours (Ware and Hopper, 1999). Of these, fewer than 3% are cardiac lymphoma (Ware and Hopper, 1999). Similarly, only 4.3% of cases presented with pancreatitis are found to be secondary to lymphoma (Cordner *et al*., 2015). In this case, it was most likely that the neoplasm had a nodal origin before metastasising to multiple organs including the bone marrow.

The diagnosis of CL involves cytology and histology in combination with immunophenotyping using immunohistochemistry, immunocytochemistry or flow cytometry to classify CL according to the REAL/ WHO classification system (Seelig *et al*., 2016). Cytology is generally accepted as a reliable initial diagnostic procedure for CL. (Carter and Valli, 1988; Carter *et al*., 1986; Sözmen *et al*., 2005). In the present case, the dog rapidly deteriorated and died while the owners were considering fine-needle aspiration (FNA) of the lymph nodes and ultrasound-guided FNA of the visceral organs. However, a diagnosis of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) was made based on the histopathology and immunophenotyping given the presence of CD3 immunolabeling of neoplastic large lymphocytes.

In this case, only supportive treatment including analgesic drugs, antiemetic drugs, intravenous glucose and crystalloid fluids were administered as the dog rapidly deteriorated to death. The mainstay treatment for lymphoma is chemotherapy. Low-grade or indolent lymphomas are managed with no therapy or conservative therapy such as chlorambucil/ prednisone or cyclophosphamide/ prednisone, whereas high-grade lymphomas including PTCL-NOS are given multi-agent chemotherapy (Biller *et al*., 2016; Vail *et al*., 2019). The most commonly administered first-line treatment for high-grade lymphomas is CHOP-based protocols (cyclophosphamide, doxorubicin, vincristine and prednisone) with or without L-asparaginase (Regan *et al*., 2012). However, the prognosis of PTCL-NOS regardless of treatment, remains poor with a median survival time of only 162 days compared to 218 days for other types of lymphoma (range 160 - 412 days) (Valli *et al*., 2013).

The main limitation in this case was the rapid deterioration due to the invasiveness and advanced stage of the neoplasm in multiple sites, which led to a limited time for diagnostic testing and treatment planning. PTCL-NOS presenting with pancreatitis, hepatic injury and cardiac insufficiency is challenging to treat and is associated with poorer prognosis (Biller *et al*., 2016; Valli *et al*., 2013). In conclusion, this case report described a case of PTCL-NOS in a dog with systemic dissemination to atypical sites including the heart and abdominal organs. As CL has a wide variety of presentations, this case demonstrated that disseminated lymphoma should always be considered in dogs presenting with nonspecific multisystemic diseases.

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