

Review Article

<https://doi.org/10.20546/ijcmas.2020.911.258>

Comparative Studies on Lymphadenopathies in Canines and Bovines

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ABSTRACT

Keywords

Bovines, Canines,
Cytology,
Lymph node,
Lymphadenopathies

Article Info

Accepted:
20 October 2020
Available Online:
10 November 2020

Lymphadenopathy referred as lymph node enlargement is the most common problem in dogs, may be due to inflammatory or non-inflammatory conditions including neoplasm. In case of cattle and buffalo, Theileriosis showed lymph node enlargement as the most common complaint. It is not a specific disease entity but an important clinical finding; the cause should be ascertained to attempt treatment and prognosis. Enlargement of lymph nodes often occurs following the proliferation of resident normal cells or infiltration of outside normal or abnormal cells. Rarely, this enlargement can be caused by vascular changes (congestion, vascularization, and edema). Common causes of lymphadenopathy include neoplasia (lymphosarcoma and metastatic neoplasia), hyperplasia or reactive lymphadenopathy, lymphadenitis (neutrophilic, purulent, eosinophilic, pyogranulomatous, or granulomatous), immune stimulation, and extra medullary hematopoiesis. Lymph node cytology is an excellent way to evaluate a lymphadenopathy whether it is a single node enlarged, multiple nodes enlarged, or a generalized lymphadenopathy. This review, therefore, provides an overview of the various conditions that are associated with lymphadenopathies in canines and bovines.

Introduction

Lymphadenopathy is a commonly encountered condition in canines. It is not a specific disease entity but an important clinical finding; the cause should be ascertained to attempt treatment and prognosis (Thangapandiyan and Balachandran, 2010). Lymphadenopathy referred as lymph node enlargement is the most common problem in dogs, may be due to inflammatory or non-inflammatory conditions including neoplasm (Thangapandiyan and

Balachandran, 2014). Lymph node enlargement, referred to as lymphadenopathy, is a frequently encountered problem in veterinary patients. Evidence suggests that cytology serves as a very useful tool in the diagnosis of two common conditions viz., cutaneous/subcutaneous masses and lymphadenopathies in veterinary patients (Villiers and Dunn, 1998). Moreover cytological techniques have become an integral part of diagnosis in clinical cases of malignancy (Roszel, 1981). Being a simple and rapid procedure, the technique employs

few resources to obtain the representative cells from most lesions. Although it is not possible to gain information on the tissue architecture, the cellular components, neoplastic and non-neoplastic cells could be interpreted clearly with the help of cytology (Morris and Dobson, 1992).

The following conditions are associated with lymphadenopathies in canines and bovines

Canines

Seasonal diseases such as ehrlichiosis and leishmaniasis should be considered a potential cause of the lymphadenopathy in regions where they are endemic, as well as in animals that have visited these areas (Gopegui *et al.*, 2004). In dogs, frequent cause of lymphadenopathy was lymphoma (Day and Whitbread 1995). In one study infectious agent induced lymphadenopathies in dogs were studied. They reported *T. evansi* in the lymph node cytology smears indicating heavy trypanosomiasis. Lymphocytic cytoplasm showed Morula and elementary bodies of *Ehrlichia* species. Both extracellular and intra neutrophilic gamonts of *H. canis* were also found in the lymph node cytology smears (Thangapandiyani and Balachandran, 2013). In dogs, cutaneous mast cell tumors in the inguinal regions frequently metastasized to abdominal lymph nodes (Allenman and Bain, 2000). Other lymphadenopathies include cystic masses, mineral-associated lymphadenopathy (Day and others 1996), systemic histiocytosis, plexiform vascularisation (Welsh and others 1999), haemangioma and lymphangioma (Hogenesch and Hahn 1998).

Lymphoma

Neoplasia of the lymphoid system is one of the most common malignancies of domestic

animals (Jarret *et al.*, 1966). Canine lymphoma has often been proposed as an animal model of its human counterpart, the non-Hodgkin's lymphomas (NHL), for it is a spontaneous tumour in a non-inbred species that shares the environment of man (Strandstrom and Bowen 1982). Study on dogs suffering from lymphoblastic leukemia showed generalized peripheral lymphadenopathy and pyrexia. Here, diagnosis of lymphoma was made by cytology and tissue core biopsy (Thangapandiyani *et al.*, 2013). Day and Whitbread 1995 reported that the mean age of dogs with lymphoma was 7.5 + 2.8 years. Mild anaemia observed in this study was a common finding as also reported by (Teske 1994). Hypercalcemia and high BUN values observed in this study in lymphoma were best documented by Weller *et al.* 1982. Gopegui *et al.* (2004) observed that lymph node enlargement is a common clinical sign in canine and feline patients which may reflect a variety of underlying disorders. In such cases it is necessary to distinguish between lymphoma or metastatic neoplasia, and other causes of lymphadenopathy, such as reactive hyperplasia or lymphadenitis, in order to institute appropriate therapy and establish a prognosis. They were of the opinion that seasonal diseases such as ehrlichiosis and leishmaniasis should be considered a potential cause of the lymphadenopathy in regions. In addition, they also suggested that the extent of the lymphadenopathy (solitary, regional or generalised) and the presence of additional lesions or abnormalities should be recorded. Thangapandiyani *et al.*, (2013) evaluated the rate of incidence, age of occurrence and serum biochemical changes in dogs with lymphoma. The results showed generalized peripheral lymphadenopathy and pyrexia. Diagnosis of lymphoma was made by cytology and tissue core biopsy. They reported lower incidence rate and the mean +

SE age of dogs (8.25 + 0.64). The affected dogs also had a severe anaemia. In addition, hypercalcemia and high BUN values were observed in lymphoma.

Lymphosarcoma in dogs

Weller *et al.*, (1982) analysed twenty-four dogs with lymphosarcoma accompanied by hypercalcaemia and studied clinical, haematological and biochemical parameter. Male dogs were more frequently affected than female dogs. Anorexia, weight loss, muscular weakness, depression, polydipsia, polyuria, and bilateral peripheral lymphadenopathy were the most frequently observed clinical signs and physical findings. Hypercalcaemia, creatinaemia, azotaemia, hypercalciuria, hyposthenuria, and decreased endogenous creatinine clearance were the most frequent laboratory abnormalities. Detailed gross and histopathologic examinations revealed the multicentric anatomic form of lymphosarcoma, absence of skeletal metastases, and normal parathyroid glands. Histologic staging revealed five diffuse histiocytic lymphomas, and five diffuse lymphocytic poorly differentiated lymphomas.

Haematopoiectumours those originating from the lymphatic tissues in dogs

Teske *et al.*, (1994) analysed that the haematopoiectumours, in particular those originating from the lymphatic tissues, are among the most frequently occurring neoplasms in the dog. They proposed canine lymphoma as an animal model of its human counterpart, the non-Hodgkin's lymphomas (NHL) as it is a spontaneous tumour in a non-inbred species that shares the environment of man. Thangapandiyan and Balachandran (2010) reported that lymphadenopathy is a commonly encountered condition in canines. They made cytological diagnosis from 109

cases and observed 52 reactive hyperplasia, 25 neutrophilic lymphadenitis, 15 eosinophilic lymphadenitis, 12 metastatic lymphadenopathies, 4 lymphomas and 1 plasmacytoma. They concluded that the FNAB technique and Romanowsky's stains were found to be the easy and rapid methods for lymph node sampling and staining respectively.

The cytologic patterns in LNs of dogs with different phases of canine monocytic ehrlichiosis (CME)

Mylonakis *et al.*, (2011) compared the cytologic patterns in LNs of dogs with different phases of canine monocytic ehrlichiosis (CME), to investigate the association of cytologic pattern and presence of Ehrlichia spp. morulae, and compared the patterns of lymphoid reactivity between dogs with CME and those with non-infectious causes of lymphoid hyperplasia. They reported that dogs with myelosuppressive CME have more lymphoid cytologic abnormalities than dogs with nonmyelosuppressive CME. They were of the opinion that LN plasmacytosis is the major pattern of lymphadenopathy in dogs with CME and was found more frequently in dogs with CME than in dogs with non-infectious causes of lymphadenopathy. de Castro *et al.*, (2004) revealed pale mucous membranes, generalized lymphadenopathy, splenomegaly, edema and ascites in dogs having CME. Microscopically, the main lesions were: lymphoreticular hyperplasia in cortical areas of lymph nodes and splenic white pulp, periportal accumulation of mononuclear cells and centrolobular fatty degeneration of the liver.

Infectious agents Induced Lymphadenopathies in Dogs

Thangapandiyan and balachandran (2013) studied the Infectious agents Induced

Lymphadenopathies in Dogs. Lymphadenopathy is a commonly encountered problem in canine practice. They reported *T. evansi* in the lymph node cytology smears indicating heavy trypanosomiasis. Lymphocytic cytoplasm showed Morula and elementary bodies of *Ehrlichia* species. Both extracellular and intra neutrophilic gamonts of *H. canis* were also found in the lymph node cytology smears in dogs having lymphadenopathies.

Bovines

Lymph node enlargement in bovine Theileriosis

In case of a cow which had generalized lymph node enlargement, cachexia, severe signs of anemia and decreased milk production. Analysis of the hemogram, revealed severe non regenerative anaemia, as evidenced by markedly decreased RBC count, PCV and haemoglobin concentration and no evidence of polychromasia and basophilic stippling. Severe leukopenia was also present. Romanowsky stained Imprints of the prescapular lymph nodes revealed trypomastigotes of *Trypanosoma vivax* among the RBCs and lymphocytes (Salgado *et al.*, 2011). Theileriosis is a tick borne blood protozoan disease caused by various *Theileria* species affecting cattle and buffaloes (Brown 1990). The affected animals show fever, anemia, enlargement of lymph nodes, anorexia and progressive loss of body weight (Gill *et al.*, 1977; Aulakh and Singla 2006). Koch's blue bodies were observed in the proliferating lymphocytes as well as extra cellularly in the affected lymph nodes (Gupta *et al.*, 2017). Chronic lymphatic leukemia was observed in cows, sheep and goats suffering from Enzootic bovine leukemia caused by bovine leukemia virus. It was characterized by long lasting lymphocytosis (Burny *et al.*, 1985). Gill *et al.*, (1977) observed the symptoms and pathology of experimental

bovine tropical theileriosis (*Theileria annulata* infection). They reported enlargement of local lymph gland, fever, haemorrhages on visible mucous membranes. They also observed anaemia and jaundice particularly in subacute and chronic forms of the disease. Post-mortem findings reported were oedema, enlargement and haemorrhages in lymph glands. The microscopic lesions were characterized by hyperplasia of lymphoid cells at the haemopoietic centres in lymph glands and spleen followed by regression and degeneration of the germinal centres. Gupta *et al.*, (2017) studied the Molecular and pathological studies on natural cases of bovine theileriosis. They conducted studies on 32 cases of bovine lymphadenopathies. They collected samples from affected lymph nodes which confirm *Theileria annulata* infection in five out of six cases. They concluded that pathological studies and cytokine analysis of lymph nodes are of paramount importance in disease diagnosis and associated immune response of the animal with lymphadenopathies.

Lymphosarcoma in heifer

Dagleish *et al.*, (1991) reported a typical case of lymphosarcoma in heifer. A clinical diagnosis of lymphosarcoma (sporadic bovine leucosis) was derived from a fine needle aspiration of a skin lesion. Post mortem and histopathological examination confirmed a multicentric lymphosarcoma with widespread infiltration into many tissues recognised as predilection sites for this type of tumour. In case of cutaneous lymphosarcoma in heifers, the mandibular, prescapular, prefemoral and supramammary lymph nodes were all enlarged (Marshak *et al.*, 1966). Enlargement of lymph node was reported and the hematologic analysis revealed mild neutrophilic leukocytosis, and monocytosis compatible with a chronic inflammatory response (Dubreuil *et al.*, 1988).

Lymphadenopathy in a cow with severe anemia

Salgado *et al.*, (2011) studied lymphadenopathy in a cow with severe anemia. They observed that the cow had generalized lymph node enlargement, cachexia, severe signs of anemia, and decreased milk production. Analysis of the hemogram revealed severe non regenerative anemia, as evidenced by markedly decreased RBC count and haemoglobin concentration and no evidence of polychromasia and basophilic stippling. Severe leukopenia was also present. The cow was euthanized, and a necropsy was performed. Severe pallor of mucous membranes, body wall, and musculature and moderate serous fat atrophy were noted. Imprints of the prescapular lymph nodes were prepared, and the slides were stained with a quick Romanowsky stain. They concluded that *Trypanosoma* species and other protozoan and rickettsial organisms, such as *Babesia* species and *Anaplasma* species were important as they cause diseases with similar clinical signs. Hajihassani *et al.* 2020 reported various species of *Trypanosoma* parasites to infect several wild and domestic animals worldwide. Physical examination revealed fever, enlarged subscapular lymph node, and pale mucosa, regenerative anemia, and progressive weight loss has been revealed in sporadic clinical cases in domestic animals.

Diagnostic aspect for lymphadenopathies

Fine-needle aspiration (FNA) cytology

Among the diagnostic tests, fine-needle aspiration (FNA) cytology is considered as an appropriate procedure in terms of its potential complications, time required, expense, sensitivity and specificity (Teske *et al.*, 1994; Langenbach *et al.*, 2001). Lymph node FNAC is a valuable tool in small animal practice, and

a simple and safe procedure to diagnose the cause of lymphadenomegaly (Gopegui *et al.*, 2004). As a result, FNA cytology has been considered a reliable method of evaluating metastasis in the regional lymph nodes in dogs and cats with solid tumours (Langenbach *et al.*, 2001). Thangapandiyar and balachandran (2014) compared the cytological and histopathological techniques in the diagnosis of canine lymphadenopathies. A total of 29 Fine Needle Aspiration Biopsy (FNAB) samples and 21 tissue samples were collected from dogs with the complaint of lymphadenopathy. They observed 77.78% of carcinomas and 50% of sarcomas were identified on lymph node cytological smear and 57.14% of carcinomas on histological sections. The correlation found between the cytomorphological findings and histopathological features clearly substantiated the usefulness of cytology in the differential diagnosis of lymphadenopathies. They were of the opinion that FNAB technique was highly sensitive in detecting metastatic lymphadenopathies. Langenbach *et al.*, (2001) determined Sensitivity and specificity of methods of assessing the regional lymph nodes for evidence of metastasis in dogs and cats with solid tumors. They suggested that fine-needle aspiration may be a sensitive and specific method of evaluating the regional lymph nodes in dogs and cats with solid tumors, because results correlated well with results of histologic examination of the entire lymph node. The tumors included 18 sarcomas, 16 carcinomas, 7 mast cell tumors, and 3 other tumors. Carcinomas were more likely to have metastasized to the regional lymph node than were sarcomas.

Air dried FNAB smears yield cells with optimal cytoplasmic and nuclear details (Morris and Dobson, 1992). The nuclear and nucleolar details were sufficient to differentiate neoplasia and inflammation and

for cytological evidence of malignant potential with Romanowsky's stain (Meinkoth and Cowell, 2002). When air dried cells were stained with Haematoxylin and Eosin (H&E) there was marked loss of nuclear details when compared with the cells that were rehydrated or immediately fixed with 95% ethanol (Lumsden and Baker, 2000)

MRI and AUS for detection of abdominal lymphadenopathy

Anderson *et al.*, (2015) compared the abdominal ultrasound and magnetic resonance imaging for detection of abdominal lymphadenopathy in dogs with metastatic apocrine gland adenocarcinoma of the anal sac. The data suggested that MRI is more sensitive than abdominal ultrasound (AUS) for detecting sacral abdominal lymphadenopathy in dogs with apocrine gland adenocarcinoma of the anal sac (AGAAS). (Stahle *et al.*, 2019) diagnosed dogs with solid tumors, regional lymph node involvement or evidence of distant metastasis which can predict worse prognoses and significantly decreased survival. Lymph node size alone has been shown to be insufficient as a predictor for the accurate clinical staging of some canine neoplasia. They evaluated diffusion-weighted MRI and ADC as potential methods for detecting metastatic lymph nodes in dogs with naturally occurring disease.

Radiographic visualization for the detection of lymphadenopathy

Murphy *et al.*, (2018) determined the efficacy of radiographs for the detection of sublumbar lymphadenopathy and identified radiographic changes that suggested nodal enlargement. They reported that radiographic visualisation of sublumbar lymph nodes was associated with marked enlargement (>17 mm), which should raise suspicion for metastatic

infiltration. However, lack of visualisation does not exclude mild to moderate lymphadenopathy and further imaging is to be warranted. The thoracic and abdominal radiographs of dogs with multilcentric lymphoma were examined to identify the radiological abnormalities. The absence of radiological abnormalities proved as a positive prognostic indicator but, in general, radiology had no place as a prognostic Indicator for the Individual patient (Blackwood *et al.*, 1997).

In conclusion the lymphadenopathy refers to the enlargement of lymph nodes. This is a frequent clinical problem. Infection, autoimmune disorders, and neoplasms can induce lymphadenopathy. Enlargement of lymph nodes is a common clinical finding with a wide range of underlying disease states. Lymphadenopathy may involve peripheral (palpable) lymph nodes and/or internal visceral lymph nodes. Lymphadenopathy may be localised (solitary or regional) or generalized in distribution. It might also encompass situations where lymph nodes are reduced in size, for example in senility, cachexia, primary immunodeficiency disease or with viral infection or immunosuppression that depletes lymphoid tissue. Further, lymph nodes might display pathological change (e.g., the presence of metastatic tumour) without necessarily being enlarged. Lymphnode FNA cytology is to diagnose the cause of lymphadenopathy.

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How to cite this article:

Avantika Sharma. 2020. Comparative Studies on Lymphadenopathies in Canines and Bovines. *Int.J.Curr.Microbiol.App.Sci.* 9(11): 2172-2180. doi: <https://doi.org/10.20546/ijemas.2020.911.258>