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REVIEW ARTICLE

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ABSTRACT

Canine lymphoma (cL) is a common type of neoplasia in dogs with an estimated incidence rate of 20–100 cases per 100,000 dogs and is in many respects comparable to non-Hodgkin lymphoma in humans. Although the exact cause is unknown, environmental factors and genetic susceptibility are thought to play an important role. cL is not a single disease, and a wide variation in clinical presentations and histological subtypes is recognized. Despite this potential variation, most dogs present with generalized lymphadenopathy (multicentric form) and intermediate to high-grade lymphoma, more commonly of B-cell origin. The most common paraneoplastic sign is hypercalcemia that is associated with the T-cell immunophenotype. Chemotherapy is the treatment of choice and a doxorubicin-based multidrug protocol is currently the standard of care. A complete remission is obtained for most dogs and lasts for a median period of 7–10 months, resulting in a median survival of 10–14 months. Many prognostic factors have been reported, but stage, immunophenotype, tumor grade, and response to chemotherapy appear of particular importance. Failure to respond to chemotherapy suggests drug resistance, which can be partly attributed to the expression of drug transporters of the ABC-transporter superfamily, including P-gp and BCRP. Ultimately, most lymphomas will become drug resistant and the development of treatments aimed at reversing drug resistance or alternative treatment modalities (e.g. immunotherapy and targeted therapy) are of major importance. This review aims to summarize the relevant data on cL, as well as to provide an update of the recent literature.

1. Introduction

Lymphoma is among the most frequently diagnosed malignancies in the dog and represents the most commonly managed neoplasia in veterinary medical oncology. Although ultimately only a small proportion of dogs with lymphoma is truly cured, the vast majority of cases can be successfully managed with chemotherapy for a prolonged period of time. This review aims to provide the veterinary practitioner with an update on the current knowledge of this disease including epidemiology, clinical picture, diagnostics, and treatment options.

2. Epidemiology

Although canine lymphoma (cL) is often viewed as a single disease, it actually comprises a number of clinically and morphologically distinct forms of lymphoid cell neoplasia. Nevertheless, cL represents the most common hematopoietic neoplasia in dogs with an estimated minimal annual incidence rate of 13–114 per 100,000 dogs (Dorn, Taylor, Hibbard 1967; Teske 1994; Dobson et al. 2002). Over the past decades, the incidence of cL has increased, and with a similar trend being observed in humans (Cartwright et al. 1999; Howlader et al. 2012); it is conceivable that common (environmental) risk factors might exist for both species (Pastor et al. 2009). Besides the reported increase in incidence in both species, many other similarities exist between cL and human non-Hodgkin lymphoma (NHL) including clinical presentation, molecular biology, treatment, and treatment response (Teske 1994; Vail and MacEwen 2000). The fact that dog breeds represent closed gene pools and the dog's genome has been sequenced, combined with the willingness of pet owners to treat their dogs for this disease, make cL a promising spontaneous large-animal model for human NHL.

Although cL can affect any dog breed, middle-sized to larger dog breeds are overrepresented (Table 1) (Teske et al. 1994b; Edwards et al. 2003; Villamil et al. 2009). This finding could not be related to growth hormone levels (Lantinga van Leeuwen et al. 2000) and more likely reflects a genetic susceptibility in some of the larger dog breeds. A familial occurrence or clustering has been reported in a few breeds including the bullmastiff (Onions 1984), Rottweiler (Lobetti 2009; Teske et al. 1994b) and Scottish terrier (Teske et al. 1994b). It was also demonstrated that some dog

Table 1. Breed with an increased and decreased risk for developing lymphoma (Edwards et al. 2003; Teske et al. 1994b; Villamil et al. 2009).

Increased risk	Decreased risk
Basset hound, Bernese mountain dog, Bouvier des Flandres, boxer, bulldog, bullmastiff, cocker spaniel, Doberman pinscher, German shepherd, golden retriever, Irish wolfhound, Labrador retriever, rottweiler, Saint Bernard, Scottish terrier	Chihuahua, dachshund, pomeranian, poodle (miniature and toy), Yorkshire terrier

breeds are more prone to developing a specific immunophenotype of cL, which further supports a genetic background (Modiano et al. 2005; Pastor et al. 2009).

Lymphoma can be diagnosed at any age, but predominantly affects middle-aged to older dogs with the incidence rate increasing with age from 1.5 cases per 100,000 dogs for dogs <1 year of age to 84 per 100,000 for dogs >10 years (Dorn et al. 1967). There is no apparent sex predisposition, but intact female dogs appear to have a reduced risk (Villamil et al. 2009) and early (<1 year) neutralization has been suggested to increase the risk of developing cL in the golden retriever (Torres de la Riva et al. 2013) and vizsla (Zink et al. 2014), but not in the Labrador retriever (Hart et al. 2014). This observation might be similar to that in humans where premenopausal women have the lowest risk for developing NHL. Despite this potential effect of sex and the likely role of sex steroids therein, both progesterone and estrogen receptors are infrequently expressed on neoplastic lymphocytes (Teske et al. 1987).

3. Etiology

Although no definitive cause for cL has been established, living in industrial areas and exposure to (household) chemicals (Gavazza et al. 2001; Takashima-Uebelhoer et al. 2012), living near waste incinerators, radioactive or polluted sites (Marconato et al. 2009b; Pastor et al. 2009), and exposure to magnetic fields (Reif et al. 1995) were all shown to increase the risk of developing cL. Although exposure to the herbicide 2,4-dichlorophenoxyacetic acid was initially linked to cL (Hayes et al. 1991; Reynolds et al. 1994), this was later revoked following reanalysis of the original data (Kaneene and Miller 1999). Further evidence that environmental toxins might play a role in carcinogenesis comes from the observation that defective genotypes of the detoxifying enzyme glutathione-S-transferase (GST), and GST theta 1 (GSTT1) in particular, are over-represented in human cancers. Of the 27 GSTT1 variants identified in the dog, one genotype was found to be present in 18% of all cL cases and the observed mutation was predicted to affect mRNA splicing and, as a result, enzyme expression and activity (Ginn et al. 2014).

Failure to repair DNA damage, resulting, for instance, from oxidative stress or radiation, increases the risk for developing neoplastic diseases and it was found that golden retrievers with cL had a lower capacity for DNA damage repair compared to golden retrievers without cL or mixed-breed dogs (Thamm et al. 2013).

Many animal species have a species-specific leukemia virus, which makes the existence of a canine 'lymphoma' virus likely. Although reverse-transcriptase activity was reported in supernatants of lymph node cultures from dogs with cL (Tomley et al. 1983) and a gamma-herpes (Epstein−Barr) virus has been detected in a proportion of cL cases (Chiou et al. 2005; Huang et al. 2012; Milman et al. 2011), a viral etiology is still not generally accepted. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma in humans is associated with *Helicobacter* infections, but experimental infections in beagles did not result in gastric lymphoma (Rossi et al. 1999).

A dysfunctional immune system could play a role in lymphomagenesis and, in humans, immunosuppression (for instance, due to HIV infection or immunosuppressive therapy for organ or stem cell transplantation), autoimmune disease or immunodeficiency disorders increase the risk of developing lymphoma. There are few data to support this theory in the dog, although autoimmune diseases are frequently reported in dogs with cL (Keller 1992), and there is a single case report of a dog that developed cL following cyclosporine treatment (Blackwood et al. 2004). A case-control study in dogs with cutaneous lymphoma (*mycosis fungoïdes*) documented an increased risk for dogs that had been diagnosed with atopic dermatitis (Santoro et al. 2007). A similar observation was made in humans and there it was suggested to result from immunodysregulation, either due to the atopic dermatitis itself, or from its immunosuppressive therapy.

4. Molecular biology of canine lymphoma

Many forms of both B- and T-cell lymphomas in humans have specific genetic abnormalities which can be used for both diagnostic and prognostic purposes (Kluin and Schuuring 2011). Although similar techniques are currently being applied to cL (Frantz et al. 2013; Richards et al. 2013; Elvers et al. 2015), the information on the molecular biology is still limited.

Comparative genomic hybridization has demonstrated limited genomic instability in cL compared to human NHL with most copy-number abnormalities in dog chromosomes 13 and 31 (corresponding to

human chromosomes 8 and 21) (Hahn et al. 1994; Thomas et al. 2011). Although gain of dog chromosome 13 appears a consistent finding in cL, it was also found in other neoplasms (Winkler et al. 2006; Thomas et al. 2009) suggesting a role in general tumor progression, rather than cL initiation.

The proto-oncogene c-kit, a tyrosine protein kinase, is an important factor in the proliferation, survival, and differentiation of hematopoietic stem cell including mast cells. The expression of c-kit in cL is typically low, but was found to be increased in some high-grade T-cell lymphomas (Giantin et al. 2013). Mutations in the N-ras oncogene are common in leukemia (Usher et al. 2009), but rare in cL (Edwards et al. 1993; Mayr et al. 2002).

Mutations in the tumor suppressor gene *p53* are relatively rare in cL (Veldhoen et al. 1998; Tomiyasu et al. 2010) and although p53 expression is typically absent or of low intensity (Sueiro et al. 2004; Sokolowska et al. 2005), expression appears more common in older animals, high grade, and possibly T-cell lymphomas (Sueiro et al. 2004). Increased Rb (retinoblastoma) phosphorylation and subsequent activation of CDK4, is common in high-grade canine T-cell lymphoma and might result from deletion of p16/loss of dog chromosome 11 (Fosmire et al. 2007), hypermethylation of the CpG island of the p16 gene (Fujiwara-Igarashi et al. 2014), and possibly from a deletion of the p15−p14−p16 locus (Fujiwara-Igarashi et al. 2013). Increased Rb phosphorylation in high-grade canine B-cell lymphoma appears to correlate with c-Myc overexpression and trisomy of dog chromosome 13 (Fosmire et al. 2007).

The Bcl-2 family consists of approximately 25 proteins that regulate apoptosis through controlling the formation of the mitochondrial outer membrane permeabilization pore (MOMPP). The canine anti-apoptotic *Bcl-2* (B-cell lymphoma 2) (Chaganti et al. 1992) was not consistently upregulated in canine B-cell lymphoma cases (Tomiyasu et al. 2010). Loss-of-function mutations and/or deletions in the tumor suppressor genes, *PTEN* and *CDKN2A/B*, have, respectively, not been studied in cL or not been found (Hahn et al. 1994; Thomas et al. 2011).

The *Bcl-6* gene encodes for a transcription factor that contributes to the development of human DLBCL. Both *Bcl-6* mRNA and protein expression were low or absent in canine high-grade B-cell lymphoma and, in contrast to the situation in humans, failed to predict clinical outcome (Sato et al. 2011b; Sato et al. 2012). The tumor suppressor gene tissue factor pathway inhibitor 2 (TFPI-2) is associated with inhibition of tumor invasion and hypermethylation of the gene and subsequent downregulation of TFPI-2 expression was identified in most canine high-grade B-cell lymphomas (Ferraresso et al. 2014).

Whole-genome and whole-exome sequencing of human diffuse large B-cell lymphoma (DLBCL) cases, the most common form of human NHL, identified 322 recurrently mutated cancer genes that included pathways related to chromatin modification, NF-κB, phosphoinositide 3-kinase (PI3K), B-cell lineage, and Wnt signaling (Zhang et al. 2013). Canonical activation of NF-κB, a regulator of genes that control cell proliferation and apoptosis, and increased NF-κB target gene expression was demonstrated in a subset of dogs with B-cell lymphoma (Gaurnier-Hausser et al. 2011; Mudaliar et al. 2013; Richards et al. 2013) and, furthermore, the proteasome inhibitor bortezomib was shown to reduce NF-κB expression and inhibit cell proliferation in neoplastic canine lymphoid cell lines (Kojima et al. 2013). Data on the possible role of PI3K and Wnt/β-catenin pathways in cL are as yet not reported.

5. Clinical presentation

The most common clinical presentation of cL is the so-called multicentric form that affects the peripheral lymph nodes, but extranodal forms exist and include mediastinal, abdominal (gastrointestinal (GI), hepatic, splenic, renal), cutaneous, ocular, central nervous system, and pulmonary lymphoma. The clinical presentation of cL can be further complicated by the presence of paraneoplastic syndromes.

5.1. Multicentric lymphoma

Multicentric cL (Figure 1(a)) accounts for ±75% of all cL cases (Ponce et al. 2010; Vezzali et al. 2010) and is classified into five stages as defined by World Health Organization (WHO) (Owen 1980) (Table 2). Occasionally, lymphoma is limited to a single lymph node (stage I) or several lymph nodes in a region of the body (stage II), but generalized, non-painful lymphadenopathy (stage III) with secondary involvement of liver and/or spleen (stage IV) or blood and/or bone marrow (stage V) are more common. A substage can be added to further characterize the clinical performance of the dog using the suffix *a* to indicate the absence of systemic signs, and *b* to indicate the presence of systemic signs such as fever, weight loss, or hypercalcemia.

5.2. Mediastinal lymphoma

Thymic or cranial mediastinal cL is more common in younger dogs (Day 1997) and is almost exclusively of T-cell origin (Fournel-Fleury et al. 2002). Presenting clinical signs include dyspnea (due to the mass effect and/or pleural effusion), polyuria/polydipisia (due to hypercalcemia), or the so-called (cranial) vena cava syndrome (Figure 1(b)). This syndrome is characterized by pitting edema of the head and neck resulting from a large mediastinal mass that restricts venous return to the heart. While diagnostic imaging (radiographic, computed tomography (CT), or ultrasonographic examination of the thorax/cranial mediastinum) will demonstrate the
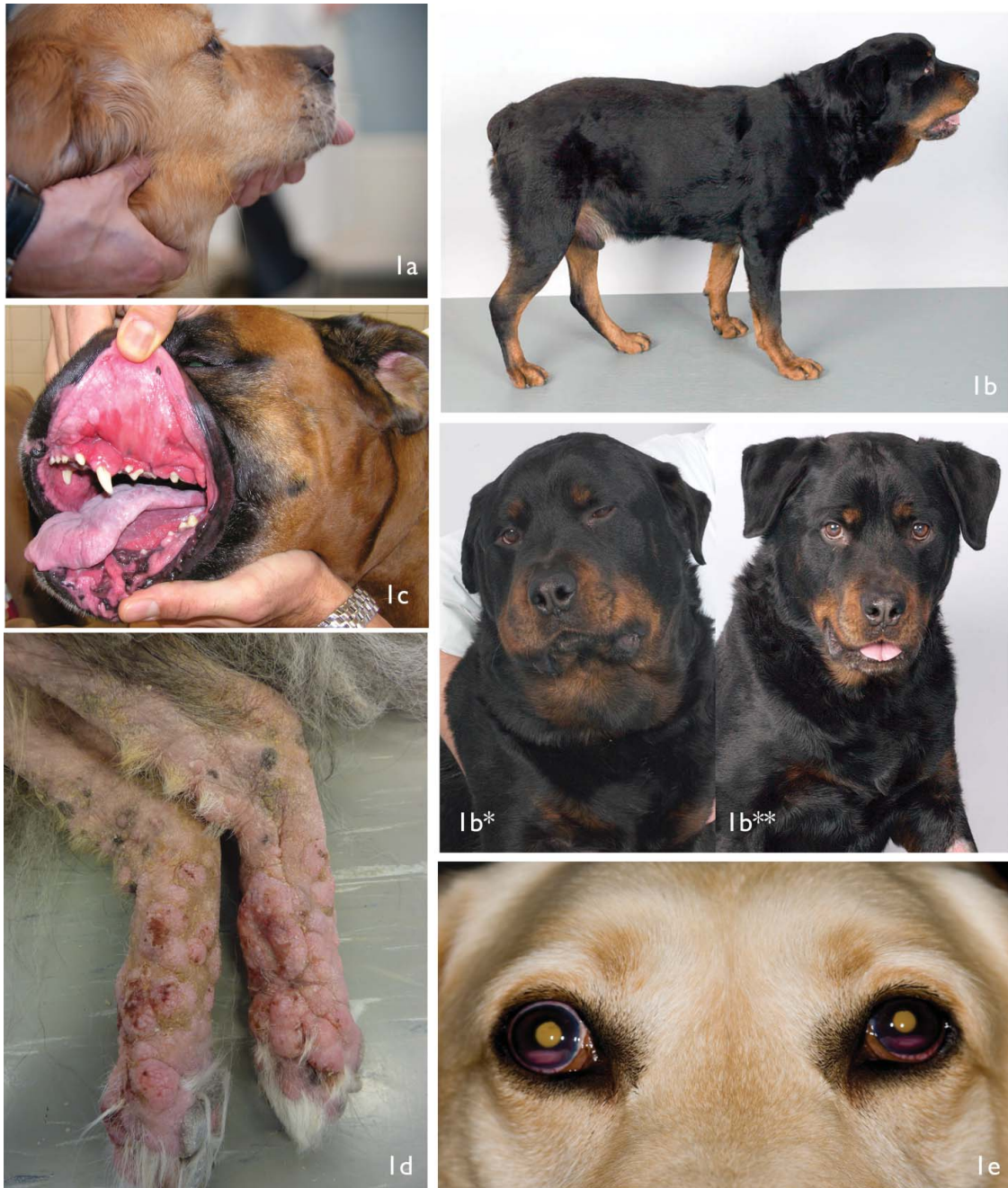
Figure 1. Clinical signs associated with canine lymphoma: lymphadenopathy (a), cranial vena cava syndrome (prior to chemotherapy b* and the same dog two days following chemotherapy b**), mucosal lymphoma (*mycosis fungoides*) (c), cutaneous lymphoma (d), and uveitis secondary to multicentric lymphoma (e).

presence of a cranial mediastinal mass (Figure 2(a)), only a cytological or histological biopsy of the mass will give the definitive diagnosis of a mediastinal lymphoma or thymoma. Although cytology is in most cases sufficient for obtaining a definitive diagnosis, immunophenotyping (Lana et al. 2006a) or PCR for antigen receptor rearrangements (PARR) (see Section 6.4) is useful when cytology is inconclusive.

Table 2. The World Health Organization (WHO) stages for canine multicentric lymphoma (Owen 1980).

Stage	
I	Single node or lymphoid tissue in single organ (excluding bone marrow)
II	Regional involvement of multiple lymph nodes (± tonsils)
III	Generalized lymph node involvement
IV	Stage I–III with involvement of liver and/or spleen
V	Stage I–IV with involvement of blood or bone marrow
Substage	
a	Absence of systemic signs
b	Presence of systemic signs (fever, >10% weight loss, hypercalcemia)
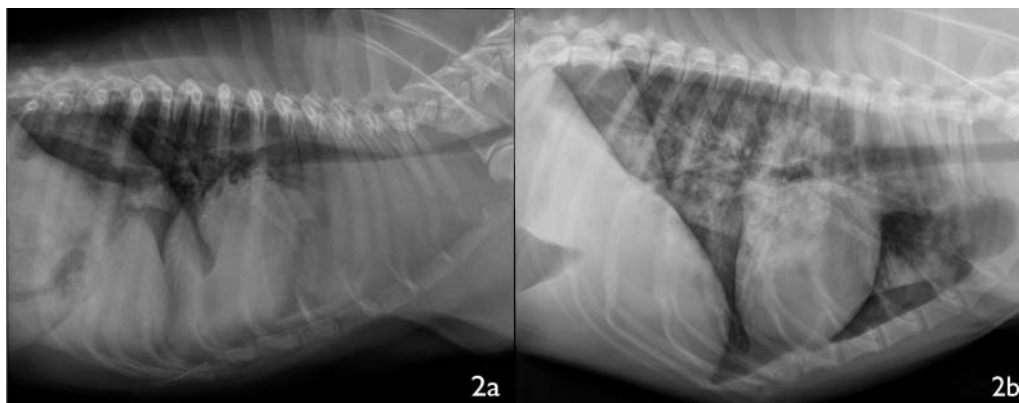
Figure 2. Left lateral thoracic radiographs of dogs with varying presentations of canine lymphoma, including a cranial mediastinal mass consistent with lymph node or thymic involvement (a) and diffuse mixed interstitial to alveolar pulmonary lung pattern in all lung lobes (b). (Courtesy of the Division of Diagnostic Imaging.)

5.3. Gastrointestinal lymphoma

GI lymphoma has no age, sex, or breed predisposition, but the boxer and shar-pei are the most commonly reported breeds (Steinberg et al. 1995; Coyle and Steinberg 2004). GI lymphoma is typically of T-cell origin (Coyle and Steinberg 2004) and can present as a solitary lesion, as multifocal (Frank et al. 2007) or diffuse disease. Ultrasonographic examination of the GI tract can be helpful in discriminating enteritis from intestinal neoplasia, but can be normal in up to 25% of dogs with GI lymphoma (Frances et al. 2013). Loss of normal wall layering, but to a lesser extent increased wall thickness, and mesenterial lymphadenopathy are suggestive for neoplasia (Penninck et al. 2003), but a definitive diagnosis will require a biopsy. In most cases, endoscopic, mucosal biopsies will be sufficient for obtaining a diagnosis (Couto et al. 1989; Miura et al. 2004), but occasionally full-thickness (transmural) biopsies (Kleinschmidt et al. 2006) or a clonality assay (PARR) (Fukushima et al. 2009; Kaneko et al. 2009) are required. A common paraneoplastic syndrome in canine GI T-cell lymphoma is local (Ozaki et al. 2006) or systemic (peripheral blood) (Marchetti et al. 2005) eosinophilia.

5.4. Hepatic lymphoma

Primary hepatic cL is relatively rare and the prognosis is poor compared to other anatomical forms of cL (Dank et al. 2011; Keller et al. 2013). Complete remission was obtained in close to half (8/18) of the dogs, resulting in a median survival of 63 days. Leukocytosis, neutrophilia, hypoalbuminemia, or hyperbilirubinemia reduced the likelihood of obtaining a complete response. Absence of complete response and hypoalbuminemia were associated with a shorter survival (Dank et al. 2011). Two forms of primary hepatic T-cell lymphoma (hepatosplenic and hepatocytotropic) have been described and both had a very poor prognosis with almost all dogs dying within 24 days after the diagnosis (Keller et al. 2013).

5.5. Cutaneous lymphoma

Cutaneous lymphoma is typically a T-cell lymphoma and more frequently epitheliotropic than non-epitheliotropic (Day 1995) (Figure 1(d)). The WHO classification recognizes three forms of cutaneous epitheliotropic T-cell lymphoma: *mycosis fungoides*, Sézary syndrome, and pagetoid reticulosis (Moore et al. 2009). There is no known cause for cutaneous lymphoma, but having been diagnosed with atopic dermatitis increases the risk for developing *mycosis fungoides* (Santoro et al. 2007). Mycosis fungoides is a CD8+ T-cell lymphoma that mainly affects older dogs (mean age 11 years) with no clear breed predilection (Moore et al. 1994c), although case series report a relatively high number of boxer dogs (Magnol et al. 1996) and Bichon Frises (Fontaine et al. 2010). Cutaneous epitheliotropic T-cell lymphoma typically presents as a chronic multifocal skin disease, but can also affect the mucous membranes (especially buccal) and mucocutaneus junctions (Moore et al. 2009) (Figure 1(c)). Skin lesions are variable in appearance and include diffuse erythema, scaling, focal hypopigmentation, plaques, and nodules (Magnol et al. 1996; Fontaine et al. 2010). Initially, the disease is limited to the skin, but later in the disease, lymphadenopathy, leukemia, and concurrent involvement of internal organs can occur, a stage that in humans is referred to as Sézary syndrome (Magnol et al. 1996).

5.6. Ocular lymphoma

Primary (peri-) ocular cL is relatively rare (<0.5% of all lymphoma cases) and cL is more commonly associated with secondary uveitis (Figure 1(e)) (Krohne et al. 1994; Massa et al. 2002). Ocular lymphoma is mostly of B-cell origin and can present both as an intraocular mass or conjunctival disease (Vascellari et al. 2005; Pate et al. 2011; McCowan et al. 2013; Ota-Kuroki et al. 2014; Wiggans et al. 2014), but can also affect extraocular structures like the palpebral conjunctiva and lymphoid

tissue of the third eyelid (Donaldson and Day 2000; Hong et al. 2011). The prognosis for conjunctival lymphoma seems better than for intraocular lymphoma, with most intraocular cases progressing to central neurologic disease (Wiggans et al. 2014).

5.7. Nervous system lymphoma

Nervous system lymphoma is relatively rare in dogs and can present both as central (brain and/or spinal cord (Dallman and Saunders 1986) including extraspinal structures (Ortega and Castillo-Alcala 2010; Veraa et al. 2010)) and peripheral nervous system disease. In case of primary brain lymphoma, cL affects only the brain and/or meninges (Couto et al. 1984; Snyder et al. 2006), while in case of secondary nervous system lymphoma both nervous and extra-nervous system locations are involved (Snyder et al. 2008). Central nervous system lymphoma typically presents as a multifocal disease and can lead to classic signs like seizures, changes in mental status, ataxia, and paresis/paralysis, but also central diabetes insipidus has been reported (Nielsen et al. 2008). Although magnetic resonance imaging (MRI) findings are not specific, a presumptive diagnosis is in most cases made by combining MRI findings with clinical information (Palus et al. 2012). A definitive diagnosis requires a cytological or histological biopsy of a mass lesion or analysis of cerebrospinal fluid showing lymphoblasts (Couto et al. 1984). In the case of secondary central nervous system lymphoma, the disease is not limited to the nervous system and a diagnosis is typically made through biopsy of an extra-nervous system site.

5.9. Pulmonary lymphoma

Pulmonary involvement in cL is common and can be both primary, as well as secondary to any other form of cL (Yohn et al. 1994). Respiratory signs are rare in cL (Starrak et al. 1997) except when it leads to pleural effusion and, in most cases, pulmonary involvement is only suggested on the basis of additional diagnostic tests (thoracic radiography, CT scan) performed for screening or staging purposes. Pulmonary lymphoma can result in alveolar, bronchial, and/or interstitial infiltrates; pleural effusion; and lymphadenopathy (Figure 2 (b)) (Geyer et al. 2010). Thoracic radiography and tracheal washes tend to underestimate pulmonary involvement compared to bronchioalveolar lavage (Hawkins et al. 1993). Since pulmonary involvement does not affect the prognosis (Starrak et al. 1997), thoracic radiographs are not recommended for routine staging.

5.10. Atypical forms of canine lymphoma

Canine lymphoma can affect any organ or location, and a wide variety of these atypical form has been reported including oral (Ito et al. 2007), periapical (Mendonca et al. 2013), nasal (Robertson 1998; Kaldrymidou et al. 2000), choanal (Shankel 2005), vertebral (Lamagna et al. 2006; Vascellari et al. 2007), skeletal (Shell et al. 1989; Dhaliwal et al. 2001), skeletal muscle (Takeuchi et al. 2010), synovial membrane (leading to ruptured cranial cruciate ligament) (Lahmers et al. 2002), adrenal (resulting in hypoadrenocorticism) (Labelle and De Cock 2005), renal (Batchelor et al. 2006; Durno et al. 2011a), urinary bladder (Kessler et al. 2008), uterine (Ko et al. 2013), prostate (Winter et al. 2006; Assin et al. 2008), cardiac, and pericardial (MacGregor et al. 2005; Aupperle et al. 2007) involvement.

5.11. Paraneoplastic syndromes

Hypercalcemia, an uncommon but well-documented paraneoplastic syndrome in the dog, is most commonly associated with cL (Messinger et al. 2009). Hypercalcemia results from the production of PTH-related peptide (parathyroid hormone [PTH]-rP) (Rosol et al. 1992) by CD4+ T-cell lymphoblasts (Ruslander et al. 1997). Hypercalcemia reduces the collecting ducts' response to antidiuretic hormone (ADH or AVP) leading to renal diabetes insipidus and increased calcium levels in the pro-urine that reduce sodium reabsorption in ascending loop of Henle, with both mechanisms contributing to polyuria. Furthermore, hypercalcemia also causes vasoconstriction of the afferent glomerular arteriole, thereby reducing the glomerular filtration rate (Kover and Tost 1993) and perfusion of renal medulla increasing the risk for hypoxia of the renal tubules (medullary thick ascending limb) (Brezis et al. 1988) and acute renal failure.

PTH-rP is not measured in the regular PTH assay and requires the use of a specific immunoradiometric assay (IRMA) (Rosol et al. 1992). However, the presence of PTH-rp can be suspected, since PTH levels are typically (extremely) low in hypercalcemia of malignancy (Mellanby et al. 2006). Although hypercalcemia is almost exclusively associated with T-cell lymphoma, it has occasionally been documented in B-cell lymphoma.

Other paraneoplastic syndromes include monoclonal gammopathy (Giraudel et al. 2002; Seelig et al. 2011; Tappin et al. 2011), hypoglycemia (Zhao et al. 1993), polycythemia in renal cL (Durno et al. 2011b), eosinophilia (Marchetti et al. 2005; Ozaki et al. 2006), and immune-mediated diseases including immune-mediated hemolytic anemia (Day 1996), immune-mediated thrombocytopenia (Keller 1992), and polymyositis (Evans et al. 2004).

6. Diagnosis

6.1. Clinical pathology

A hematological and clinical chemistry profile is routinely performed in most dogs diagnosed with cL and can show a wide range of non-specific abnormalities (Gavazza et al. 2008). Most dogs will have a mild-to-moderate non-regenerative anemia, but anemia can also arise from blood loss (GI lymphoma) or (secondary) immune-mediated hemolytic anemia (Day 1996). Increased red blood cell counts (polycythemia) have occasionally been reported in renal lymphoma (Durno et al. 2011a) and are thought to result from inappropriate erythropoietin secretion. Morphologic erythrocyte abnormalities can be observed and include schistocytes (Madewall et al. 1980), eccentrocytes (Caldin et al. 2005), and acanthocytes (Warry et al. 2013). Although leukocyte counts are typically normal, both leukocytosis and leukopenia have been described. In most cases, the leukocytosis represents an inflammatory response (neutrophilia), with leukemia accounting for approximately 20% of the leukocytosis cases (Gavazza et al. 2008). Mild, asymptomatic thrombocytopenia is common (Grindem et al. 1994), but occasionally a thrombocytosis is noted (Madewall et al. 1980; Neel et al. 2012). Most dogs with cL will show mild abnormalities in their hemostatic profile that would be consistent with hypercoagulability and these tend to persist during chemotherapy (Madewall et al. 1980; Kol et al. 2013).

Although increases in liver enzyme activities or kidney values may result from cL affecting either of these organs, they are more often secondary to cL and indicate reactive hepatopathy and dehydration. A rise in serum lactate dehydrogenase (LDH) activities, and in particular an increase in the isoenzymes LDH2 and LDH3 (Dumontet et al. 1999), is an important prognostic indicator in human NHL. While some studies (Zanatta et al. 2003; Marconato et al. 2010) reported a prognostic value for LDH and LDH isoenzyme measurement, others (Greenlee et al. 1990; von Euler, Ohrvik, Eriksson 2006; Marconato et al. 2009a) failed to demonstrate this effect and as a result it is currently not recommended to include either of these tests in the routine staging protocol for dogs with cL. Alkaline phosphatase (ALP) activities might increase following hepatic involvement, as well as previous exposure to glucocorticoids, but were nevertheless not predictive for treatment response (Wiedemann et al. 2005). Serum protein levels can decrease due to GI blood or protein loss (GI lymphoma), but also increase due to monoclonal gammopathy. Hypoglycemia has occasionally been reported in cL (Zhao et al. 1993). Hypercalcemia is documented in ±10%−15% of cL cases and is almost exclusively associated with T-cell lymphoma.

Urinalysis is not routinely performed, but proteinuria appears a common finding in dogs with multicentric cL. It is typically mild, independent of (sub-)stage and has no impact on prognosis (Di Bella et al. 2013).

Bone marrow involvement is reported in up to 55% of dogs (Raskin and Krehbiel 1989) and cannot be accurately predicted from peripheral blood counts (Martini et al. 2013). Since bone marrow core biopsies or flow cytometry of bone marrow samples are not routinely performed in veterinary medicine, cytological examination of a single bone marrow aspiration sample remains the most commonly used technique and proved sufficient for identifying bone marrow involvement (Aubry et al. 2014). Since a bone marrow biopsy is considered an invasive procedure, and the outcome has limited effect on prognosis (unless there is massive bone marrow involvement) or treatment, it is at present not advised to routinely perform a bone marrow biopsy (Vail et al. 2010).

6.2. Diagnostic Imaging

Thoracic and abdominal radiographs from dogs with (multicentric) cL will often show abnormalities, although these are typically non-specific and merely suggest cL as a possible differential diagnosis (Blackwood et al. 1997). Thoracic radiographs will reveal abnormal findings in 70% of cL cases and include thoracic lymphadenopathy, pulmonary infiltrates, and the presence of a cranial mediastinal mass (Figure 2) (Starrak et al. 1997).

Ultrasonography of the abdomen and (peripheral) lymph nodes is helpful in accurately assessing lymph node size and architecture (Figure 3(a)) (Nyman et al. 2005; Nyman et al. 2006), as well as hepatic and/or splenic involvement (Figure 3(b)) (Crabtree et al. 2010). Abdominal ultrasonography is not suitable for diagnosing or excluding GI lymphoma, since findings are either non-specific or may even be absent in as much as 25% of dogs (Frances et al. 2013).

X-ray CT scan provides excellent detail and is ideal for evaluating the extent of disease, but typically will not allow for a specific diagnosis. For instance, in the case of a cranial mediastinal mass, a CT scan is helpful for staging purposes, but not able to discriminate between a thymoma and mediastinal lymphoma (Yoon et al. 2004).

In human oncology, the combination of positron emission tomography with a CT scan, the PET-CT, has become the standard for staging many types of cancer. Veterinary medicine has limited access to this imaging modality and up to now only small case series have been published (Bassett et al. 2002; Lawrence et al. 2009; LeBlanc et al. 2009; Ballegeer et al. 2013). The use of scintigraphy using radiolabeled peptide nucleic acid−peptide conjugate targeting Bcl-2 mRNA has been described in dogs with multicentric B-cell lymphoma and was useful for assessing both the extent of disease and monitoring treatment response (Statham-Ringen et al. 2012).
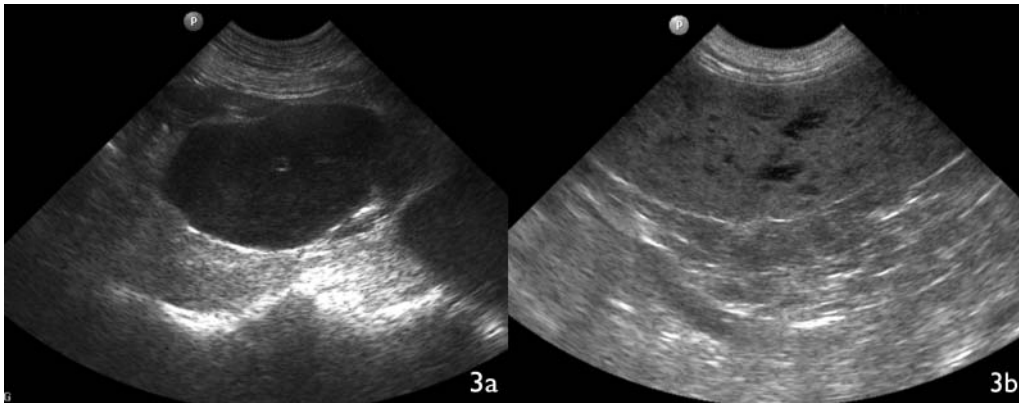
Figure 3. Abdominal ultrasonographic images showing typical findings in dogs with canine lymphoma including rounded, hypoechoic lymph nodes (a) and an enlarged spleen with multiple hypoechoic nodules, often referred to as a 'Swiss-cheese' spleen (b). (Courtesy of the Division of Diagnostic Imaging.)

### 6.3. Cytology, histology, immunophenotyping

Cytological examination of a fine-needle aspirate from a neoplastic lymph node is a quick, sensitive, and minimally invasive technique for diagnosing high-grade cL (Teske and van Heerde 1996; Sozmen et al. 2005) making it the diagnostic method of choice.

However, cytology may be insufficient for diagnosing low-grade cL (Figure 4) or characterizing atypical lymphoid proliferations. Examination of a histological biopsy will improve the diagnosis of low-grade cL, but will also allow for further subclassification of cL. An excisional biopsy (removal of a complete lymph node) is preferred, but in many cases an incisional or thru-cut biopsy is sufficient. The increased possibilities of flow cytometry to analyze fine-needle aspirates from neoplastic lymph nodes might decrease the need for excisional biopsies (Gelain et al. 2008; Comazzi and Gelain 2011).

Histologically, cL is characterized based on a number of morphological criteria including growth pattern, nuclear size, nuclear morphology (chromatin pattern, number and location of nucleoli), mitotic index, and immunophenotype. Based on these characteristics, cL is classified using one of the classification schemes that have been developed over the past decades including the Rappaport (Rappaport 1966; Teske et al. 1994a), Lukes-Collins (US) (Lukes and Collins 1974; Teske et al. 1994a), KIEL (Europe) (Lennert and Mohri 1978; Teske et al. 1994a), Working Formulation (Anonymous 1982; Carter et al. 1986), updated Kiel (Fournel-Fleury et al. 1997b; Stein et al. 1981; Teske et al. 1994a), REAL (Harris et al. 1994) and WHO (Table 3) (Harris et al. 1999; Valli et al. 2011; Valli et al. 2013).

The (updated) Kiel classification can be applied to both histological (Ponce et al. 2004) and cytological (Teske and van Heerde 1996) samples and although it has its limitations in diagnosing certain low-grade subtypes, like marginal zone lymphoma (Fournel-Fleury et al. 1997b), it is still the most commonly used classification scheme. The WHO system is based on a histological evaluation and when the human classification scheme was applied to the dog, it was found that the vast majority of lymphoma cases consisted of only five subtypes: diffuse large B-cell lymphoma (54%), marginal zone (B-cell) lymphoma (4%), peripheral T-cell lymphoma not otherwise specified (16%), nodal T-zone lymphoma (14%) and T lymphoblastic lymphoma (5%) (Table 4) (Valli et al. 2011).
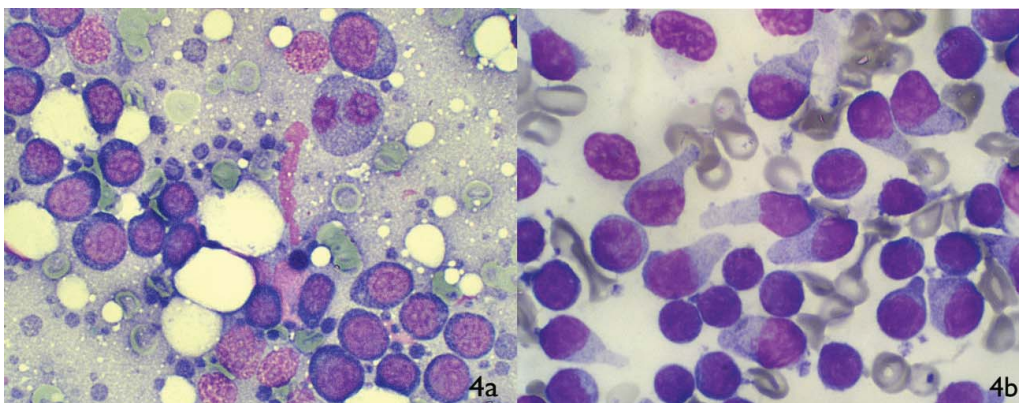
Figure 4. Microscopic pictures showing the typical cytological appearance of a high-grade lymphoma (a: diffuse large B-cell lymphoma, immunoblastic) and a low-grade lymphoma (b: lymphoplasmacytoid T-cell).

Table 3. The current canine lymphoma WHO classification and corresponding categories in the Kiel classification and working formulation (Valli et al. 2011; Vezzali et al. 2010).

		WHO classification	Working formulation	Kiel classification
B	Precursor	B-ALL/B-LBL	ALL, LBL	Lb
	Mature	B-CLL/B-SLLL	B-CLL/B-SLLL	Lc
		LLI	—	—
		LPL	SLLP	Pl
	Follicular	MCL	DSCCL	Cc
		FCCL-I	FSCCL	Cc
		FCCL-II	FMCL	Cc-Cb
		FCCL-III	FLCL	Cc
		NMZ	CLL, FSCCL, DSCCL, DMCL	Lc, Cc, Cb
		SMZ		
		MALT-L		
	Plasmacytic	PCT Indolent	Extramedullary plasmacytoma	Extramedullary plasmacytoma
		PCT Anaplastic		
		Myeloma	Multiple myeloma	Multiple myeloma
	B-LCL	DLBCL, DLBBL	DMCL, DLCL, DLCCL	Cc, Cb
		LCIBL	LCIBL	Ib
		T-cell rich B-LCL	DMCL, DLCL	Cb
		Thymic B-LCL	DMCL, DLCL	Cb
	Burkitt-type, Burkitt-like	SNCCL	—	
T	Precursor	T-ALL/T-LBL	ALL, LBL	Lb
	Mature	T-CLL/T-SLL	CL, SLL	Lc
		LGL	—	—
		NK-CLL	—	—
	Cutaneous	CEL	MF/SS or DLCL, DMCL, DSCCL	MF/SS
		CNEL	MF/SS-like or DLCL, DMCL, DSCCL	MF/SS-like
	PTCL		DSCCL, DMCL, DLCL, DLCCL	—
	ATL	ACL	DSCCL, DMCL, DLCL, DLCCL	—
		AIL		
	ITCL		DSCCL, DMCL, DLCL, DLCCL, LCIBL	—
	ALCL		LCIBL	—

Note: B- or T-ALL, B- or T-acute lymphoblastic leukemia; B- or T-LBL, B- or T-lymphoblastic lymphoma; B- or T-CLL, B- or T-chronic lymphocytic leukemia; B- or T-SLL, B- or T-small lymphocytic lymphoma; LLI, B-cell lymphocytic lymphoma of intermediate type; LPL, lymphoplasmacytic lymphoma; LGL, large granular lymphocyte lymphoma or leukemia; NK-CLL, NK-cell chronic lymphocytic leukemia; MCL, mantle cell lymphoma; FCCL, follicle center cell lymphoma; MZL, marginal zone lymphoma; NMZ, nodal marginal zone lymphoma; SMZ, splenic marginal zone lymphoma; MALT-L, mucosa-associated lymphoid tissue lymphoma; PCT, plasmacytic tumours; B-LCL, large B-cell lymphoma; DLBCL or DLBBCL, diffuse large B-cell lymphoma, cleaved or not cleaved; LCIBL, large cell immunoblastic lymphoma; CEL, cutaneous epitheliotropic lymphoma; MF/SS, mycosis fungoides/Sézary syndrome; CNEL, cutaneous non-epitheliotropic lymphoma; PTCL, extranodal or peripheral T-cell lymphoma; AIL, angioimmunoblastic lymphoma (also known as angioimmunoblastic lymphomatous disease); ATL, angiotropic lymphoma; ACL, angiocentric lymphoma; AIL, angioinvasive lymphoma; ITCL, intestinal T-cell lymphoma; ALCL, anaplastic large cell lymphoma; Lb, lymphoblastic; Lc, lymphocytic; Cc, centrocytic; Cb, centroblastic; Ib, immunoblastic; Pl, plasmacytic/plasmacytoid; F- or DSCCL, follicular or diffuse small cleaved cell lymphoma; F- or DMCL, follicular or diffuse mixed cell lymphoma; F- or DLCL, follicular or diffuse large cell lymphoma; DLCCL, diffuse large cleaved cell lymphoma; SLLP, small lymphocytic lymphoma plasmocitoid; SNCCL, small non-cleaved cell lymphoma; PCT, plasmacytoma, NOS: not otherwise specified.

Although the majority of cL cases are of B-cell origin (±70%), with a smaller proportion of T-cell (±30%) or non-B-/non-T-cell lymphomas (<5%) (Appelbaum et al. 1984; Teske et al. 1994a; Caniatti et al. 1996; Fournel-Fleury et al. 1997b; Ruslander et al. 1997), this distribution can vary significantly between canine breeds. For example, the Irish wolfhound, Shih Tzu, Airedale terrier, Yorkshire terrier, cocker spaniel, and Siberian husky are in >80% of cases of T-cell origin, while the Doberman pinscher, Scottish terrier, border collie, Cavalier King Charles Spaniel, and basset hound have in >80% of cases B-cell ML (Modiano et al. 2005), but geographical differences in B/T-distribution per breed might exist (Pastor et al. 2009).

Immunophenotyping can be slide-based and performed on cytological (Figure 5) (Caniatti et al. 1996) or histological (Milner et al. 1996) biopsy samples or by use of flow cytometry (Culmsee et al. 2001; Gelain et al. 2008), all of which show an excellent correlation (Fisher et al. 1995). The antibodies most commonly used include CD20, CD21, CD79α, and PAX5 for B-cell lymphoma and CD3, CD4, and CD8 for T-cell lymphomas (Caniatti et al. 1996). Immunophenotyping with only two antibodies (typically CD3 and CD79α or CD20) can result in as many as 20% unclassified cL cases (Guija de Arespacochaga et al. 2007). While this might be sufficient for routine patient care, increasing the number of antibodies will not only result in more conclusive immunophenotyping, but also a lower percentage of non-B/non-T lymphomas.

More recently, the use of the PARR (see Section 6.4) has been advocated as an alternative for immunohistochemistry or flow cytometry, but flow cytometry proved superior over the PARR (overall agreement between tests was 60%), although in the absence of fresh samples, the PARR can be an acceptable alternative (Thalheim et al. 2013).

6.4. PCR-based techniques

PCR-based techniques have been used for diagnosing, staging, immunophenotyping (Burnett et al. 2003;

Table 4. Overview of most commonly recognized forms of canine lymphomas (Flood-Knapik et al. 2013; O'Brien et al. 2013; Valli et al. 2013).

WHO	Updated Kiel	IPT	%	Gr	Clinical presentation	Cytology	Histology	Therapy	Survival (months)
Diffuse large B-cell lymphoma	Centroblastic, immunoblastic, polymorphic	B	54	H	MCL, ± liver, ± spleen, ± blood/bone marrow	Large cells, scant cytoplasm, uniformly large nuclei, usually round, rarely cleaved or indented, centroblastic and/or immunoblastic, mitotic figures common	Diffuse, thinning of Ln capsule, compression of peripheral and medullary sinus, fading germinal centers, destruction of normal nodal structures, filling of the medullary cords with neoplastic cells, many tingible body macrophages, high MR	(L)CHOP	±9
Marginal zone lymphoma	Medium-sized macronucleated cells (MMC)	B	4	L	Splenic or nodal	Intermediate-sized nuclei, prominent single central nucleoli, abundant lightly stained cytoplasm, no mitotic figures	Coalescing aggregates of indolent B-cells surround fading remnants of germinal centers, resembling the marginal zone of a lymph node follicle	Splenic: surgery, no CHOP; Nodal: prednisolon + chlorambucil?, no CHOP	Splenic 13, Nodal 21
Peripheral T-cell lymphoma, NOS	Pleomorphic mixed	T	16	H	MCL, ± liver, ± spleen, ± blood/bone marrow	Large to variable cell size, frequently cleaved or oval nuclei, nucleoli inconsistent in number and size, pale cytoplasm, variable mitotic figures, few tingible body macrophages	Diffuse, thin Ln capsule, paracortical expansion, sinus compressed, focally obliterated, spread of neoplastic cells to perinodal tissue. The neoplastic cells are usually large, may be of variable cell size, frequently have cleaved or oval nuclei, nucleoli inconsistent in number and size, variable MR, may lack numerous tingible body macrophages.	(L)CHOP + CCNU?	±6
T zone lymphoma	Small clear cell	T	14	L	Regional – MCL	Small cells, round nucleus, can have irregular shallow nuclear indentation, extended pale cytoplasm (hand mirror/uropods)	Uniform population of small or intermediate T-cells expanding in paracortex and medullary cords, no effacement nodal architecture, nuclei no internal nuclear detail, shallow nuclear indentation, extended pale cytoplasm	Prednisolon + chlorambucil	20-33
T-lymphoblastic lymphoma	Lymphoblastic	T	5	H	MCL, ± liver, ± spleen, ± blood/bone marrow, ± mediastinal, ± hypercalcemia	Uniform population intermediate-sized cells, evenly dispersed chromatin, obscured nucleoli	Thin capsule, focal perinodal colonization, diffuse cortical and medullary filling, moderate anisokaryosis, nuclei range from round to oval or irregularly indented, densely stained cells (dispersed chromatin) that obscures nucleoli, no tingible body macrophages, high MR	(L)CHOP+ CCNU?	6-8

Note: Gr: grade, H : High, IPT: immunophenotype, Ln: lymph node, L: Low, MCL: multicentric lymphadenopathy, MR: mitotic rate.
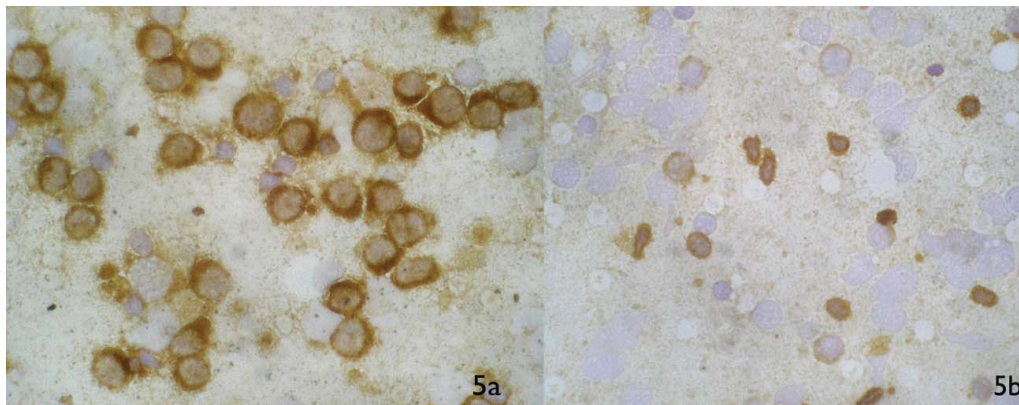
Figure 5. Microscopic pictures showing the cytological appearance of an immunocytochemical staining for CD79α (a) and CD3 (b) on a lymph node aspirate demonstrating CD79α-reactivity for the neoplastic B-cells and CD3-reactivity for the reactive (non-neoplastic) T-cells consistent with a high-grade B-cell lymphoma.

Lana et al. 2006b; Thalheim et al. 2013), and detecting minimal residual disease (MRD) (Sato et al. 2011a). The most commonly used PCR technique is the PCR assay for antigen receptor rearrangement (PARR), which amplifies the variable regions of the immunoglobulin genes and the T-cell receptors. The presence of monoclonal or oligoclonal peak is highly suggestive of cL and although this test has a high sensitivity ($\pm$75%) and high specificity ($\pm$95%), some infections (e.g. monocytic ehrlichiosis) and other neoplastic diseases (e.g. acute myeloid leukemia) can lead to false-positive results (Burnett et al. 2003). Although the PARR has been used for staging cL patients, clinical stage proved a better prognostic indicator than PARR stage and as a result is not recommended for routine staging (Flory et al. 2007). The PARR can be used for immunophenotyping, but is less accurate than antibody-based techniques and should be reserved for those cases in which there is no sample available for immunostaining or flow cytometry (Thalheim et al. 2013).

Future developments in PCR-based techniques may include the analysis of miRNA expression patterns and this technique has been used both in lymph node (Mortarino et al. 2010) and serum (Fujiwara-Igarashi et al. 2015) samples from dogs with cL. Although the initial reports appear promising, there are as yet insufficient data to draw firm conclusions with regards to their potential use in diagnosing cL or establishing a prognosis.

6.5. Biomarkers

Biomarkers are serum proteins that can be used to diagnose and/or monitor a specific disease. Acute-phase proteins, TK1, MCP-1, VEGF, MMP, and endostatin, have all been evaluated in cL based on their prior use in human oncology. More recently, serum protein electrophoresis has been used to identify potential specific canine biomarkers (Gaines et al. 2007; McCaw et al. 2007; Ratcliffe et al. 2009; Atherton et al. 2013),

but as yet there are no data on their usefulness in a clinical setting.

Measurement of haptoglobin and C-reactive protein levels has a low sensitivity and specificity for diagnosing cL and needs to be combined with clinical data in order to be useful as a diagnostic test (Mirkes et al. 2014). TK1 is a salvage enzyme involved in DNA precursor synthesis and its levels are not only higher in dogs with cL compared to healthy dogs or dogs with non-hematologic neoplasia, but also appear to correlate with stage and prognosis (Nakamura et al. 1997; von Euler et al. 2004; Elliott et al. 2011) making it the most promising biomarker currently available. There is a single study on monocyte chemotactic protein-1 (MCP-1) expression in cL and levels were higher in dogs with cL than in healthy dogs and levels also correlated with stage (Perry et al. 2011). Vascular endothelial growth factor (VEGF) and matrix-metalloproteinase (MMP) 2 and 9 are under control of transforming growth factor beta (TGF-β). Dogs with cL had a higher MMP9 activity, higher VEGF levels, and lower TGF-β levels than dogs without cL. Furthermore, MMP9 and VEGF were higher in T-cell and stage V lymphoma, and lastly VEGF expression correlated with grade in T-cell lymphomas. However, none of these parameters proved useful in predicting prognosis (Wolfesberger et al. 2012; Arico et al. 2013; Aresu et al. 2014). Endostatin prevents angiogenesis and tumor growth through inhibition of endothelial cell proliferation and migration, and tended to be higher in dogs with cL, but was not useful as a biomarker (Rossmeisl et al. 2002).

7. Staging canine multicentric lymphoma

Staging multicentric cL is done according to the WHO staging scheme (Table 1) and requires a thorough patient history (substage), physical examination (stages I–IV), and evaluation of the peripheral blood and bone marrow (stage V). Although additional laboratory tests and diagnostic imaging are recommended, it should be appreciated that increasing the number of staging

tests or choosing more sensitive staging techniques will result in more correct staging and most likely stage migration, but not necessarily in a better prediction of the prognosis (Flory et al. 2007).

Given the strong negative effect of hypercalcemia and the T-cell immunophenotype on prognosis, it is advised to include these two tests in the staging protocol. Both thoracic radiographs and abdominal ultrasonography lead to a more correct staging in multicentric cL (Flory et al. 2007), but imaging results only affect the prognosis if they document the presence of a cranial mediastinal mass (Starrak et al. 1997). Therefore, diagnostic imaging should not be routinely performed, but considered on an individual basis.

Despite the fact that bone marrow involvement has a significant effect on prognosis and cannot be predicted from peripheral blood counts (Martini et al. 2013), it has little effect on treatment and as a result a bone marrow biopsy is not routinely recommended (Vail et al. 2010).

Cytological examination of fine-needle aspirates of extranodal sites (liver, spleen, blood, and bone marrow) remains the most commonly used staging technique, but the use of the PARR (Burnett et al. 2003; Lana et al. 2006b) and flow cytometry (Joetzke et al. 2012) have been reported. PARR results often lead to

stage migration and PARR stage does not provide a better estimation of prognosis.

8. Therapy

The majority of therapy-related studies focus on the chemotherapeutic treatment of intermediate-to-high-grade multicentric cL and information on the optimal treatment for low-grade and extranodal forms of cL is limited.

8.1. Chemotherapy

Given the systemic nature of cL, chemotherapy is considered the therapy of choice. The goal is to obtain a maximum effect (high complete response rate, long response duration) with a minimum of consultations (reducing stress and discomfort for both animal and owner), drug administrations (reducing drug excretion in owner's environment), and toxicity. A comprehensive overview of the reported treatment protocols is provided in Tables 5 and 6.

8.1.1. Glucocorticoids
Glucocorticoids induce lymphocyte and lymphoblast apoptosis (Smith and Cidlowski 2010) and are routinely

Table 5. Comparison of different first-line therapy protocols reported for the treatment of canine multicentric lymphoma.

Protocol	Number of dogs	Length protocol (weeks)	CRR (%)	Median DFP (days)	Median OST (days)	1-year OST (%)	2-year OST (%)	1-year CRR (%)	2-year CRR (%)
P (Squire et al. 1973)	49	As long as response	43	531	NR	NR	NR	NR	NR
H (continuous) (Carter RF et al. 1987)	21	NR	76	206	266	NR	NR	NR	NR
H (continuous) (Simon et al. 2008)	27	15	52	309	322	20	0	77	NR
H (intermittent) (Higginbotham et al. 2013)	18	H given up to maximum dose	78	81	171	NR	NR	NR	NR
CCNU-P (Sauerbrey et al. 2007)	17	15	35	40	111	NR	NR	NR	NR
(L)CVM (MacEwen et al. 1987a)	147	As long as response	77	140	265	25	NR	NR	NR
COP (Carter RF et al. 1987)	20	As long as in CR	70	100	224	NR	NR	NR	NR
COP (Dobson et al. 2001)	49	78	76	159	224	NR	NR	NR	NR
(L)CHP (Piek, Rutteman, Teske 1999)	65	22	65	203	200	35	22	29	NR
(L)CHOP (Greenlee et al. 1990)	112	36, COP maintenance	73	238	344	NR	NR	42	28
L-CHOP Teske et al. 1994)	138	10, L-asp maintenance	84	NR	NR	42	NR	NR	NR
LCHOP (Myers et al. 1997)	68	78	65	274	301	27	13	40	21
LVCAM[2] (Keller et al. 1993)	55	135	84	220	303	52	24	42	25
LVCA-S (Garrett et al. 2002)	51	25	94	282	397	NR	NR	NR	NR
VELCAP-L (Zemann et al. 1998)	98	75	69	385[3]	517[3]	NR	NR	53	25
VELCAP-S (Moore et al. 2001)	82	15	68	140	NR	NR	NR	NR	NR
VELCAP-SC (Morrison-Collister et al. 2003)	94	21	70	168	302	44	13	17.4	15.5

Note: P = prednisolon, H = hydroxydaunorubicin or adriamycin (= A), O = oncovin or vincristine (= V), C = cyclophosphamide or Endoxan (= E), L/EL = L-asparaginase, M = Methotrexate, NR = not reported).
[1]Mean,[2]LVCAM = University Winsconsin- Madison protocol, [3]only reported for animals achieving CR.

Table 6. Comparison of different rescue chemotherapy protocols used for the treatment of canine multicentric malignant lymphoma.

Protocol	Number of dogs	Overall response (%)	Median response duration (days)	Complete response (%)	Complete response duration (days)
Actinomycin D	25	0	0	0	0
(Bannink et al. 2008; Moore, Ogilvie, Vail 1994a)	494[1]	41	129	41	129
Mitoxantrone	15		21	47	84
(Lucroy et al. 1998; Moore et al. 1994b)	44	41	127	30	NR
Dacarbazine	40	35	43	3	144
(Griessmayr et al. 2009)					
CCNU	43	27	86	7	110
(Moore et al. 1999)					
Dacarbazine—doxorubicine	15	53	45[2]	33	105[2]
(Van Vechten, Helfand, Jeglum 1990)					
Dacarbazine—anthracycline	18	72	40	50	NR
or Temozolamide—anthracycline	35	71	85	63	NR
(Dervisis et al. 2007)					
MOPP	117	65	61	31	63
(Rassnick et al. 2002)					
DMAC	54	72	61	44	112
(Alvarez et al. 2006)					
LOPP	44	52	106	27	112
(LeBlanc et al. 2006)					
BOPP	14	50	130	29	130
(LeBlanc et al. 2006)					
LOPP-CFU	33	61	98	36	NR
(Fahey et al. 2011)					
MOMP	88	51	56	12	81
(Back et al. 2015)					
MPP	41	34	56	17	238
(Northrup et al. 2009)					
L-Asparaginase—CCNU—prednisolone	31	87	63	52	111
(Saba, Thamm, Vail 2007; Saba et al. 2009)	48	77	70	65	90
CCNU — Dacarbazine	57	35	62	23	83
(Flory et al. 2008)					

Note: MOPP: mechlorethamine, vincristine, procarbazine, prednisolone; DMAC: dexamethasone, melphalan, actinomycin D, cytosine arabinoside; LOPP: CCNU, vincristine, procarbazine, prednisolone; BOPP: carmustine/BCNU, vincristine, procarbazine, prednisolone; MOMP: mechlorethamine, vincristine, melphalan, prednisone; MPP: mechlorethamine, procarbazine, prednisolone.
[1]Half the patients concurrently received prednisolone, [2]survival.

used in the treatment of cL. Most dogs will experience a good partial to complete response that typically lasts for 60−90 days (Squire et al. 1973; Bell et al. 1984) and should be considered a palliative treatment. Some studies have shown that pretreatment with glucocorticoids prior to starting chemotherapy results in lower response rates and shorter remission periods (Price et al. 1991; Teske et al. 1994; Gavazza et al. 2008; Marconato et al. 2011), and the use of glucocorticoids should be withheld until the decision has been made to not pursue treatment with cytostatic drugs.

The absence of increased prostaglandin E_2 levels (Mohammed et al. 2001) combined with no (Mohammed et al. 2004) or little (Asproni et al. 2014) COX-2 expression in neoplastic lymph nodes makes a role for (selective) COX-2 inhibitors in the treatment of cL unlikely.

8.1.2. First-line protocols

8.1.2.1. Single-agent therapy. Various single-agent therapies have been described and include a monotherapy with (PEG-)L-asparaginase (MacEwen et al. 1987b; Teske et al. 1990), doxorubicin (Carter et al. 1987; Simon et al. 2008), mitoxantrone (Lucroy et al. 1998), and CCNU (Sauerbrey et al. 2007). Of all of these protocols, a monotherapy with doxorubicin, either as a

continuous (5x q3 weeks) or an intermittent (induction followed by additional doses at the time of tumor progression) (Higginbotham et al. 2013) protocol appears most effective, but still less effective than a doxorubicin-based multi-agent protocol and should be reserved for treatments with a palliative intent.

8.1.2.2. Multi-agent therapy. Multi-agent therapy protocols are typically injection protocols that combine cyclophosphamide, doxorubicin (Hydroxydaunorubicin), vincristine (Oncovin), prednisolone (so-called CHOP), and oftentimes L-asparaginase (L-CHOP). CHOP protocols result in the highest response rate and longest response durations and form the basis for most of the current protocols used for treating high-grade cL (Table 4).

Early protocols consisted of two phases, an initial more intensive protocol aimed at inducing a complete remission (induction phase), later followed by a lifelong less intensive protocol aimed at maintaining remission (maintenance phase). It was later shown that a continuous maintenance phase following induction of a complete response offered no treatment benefit and as a result total protocol length has gradually decreased. Although a 6-month protocol, i.e. an induction phase followed by a short maintenance protocol, is considered the standard of care (Piek et al. 1999; Chun et al.

2000; Garrett et al. 2002), 12-week (Simon et al. 2006) and 15-week (Burton et al. 2013)) protocols have been reported and appear equally effective. Increasing treatment intensity, either by increasing the number of drugs, drug dosages, or shortening dose intervals, has failed to improve treatment outcome, but increases adverse events (Vaughan et al. 2007; Rassnick et al. 2010; Sorenmo et al. 2010). Adding prednisolone to a doxorubicin-based multidrug protocol does not improve treatment results and should be reserved for later use in a rescue protocol (Zandvliet et al. 2013a).

8.1.3. Rescue protocols

Rescue protocols are used in case of failure to respond to a first-line protocol or following relapse and include both single-agent and multi-agent protocols. The choice of treatment protocol varies depending on the moment of relapse in relation to the original (first-line) protocol, previously used drugs (e.g. cumulative cardiac toxicity of doxorubicin), and individual clinician's preferences. With respect to the moment of relapse, a relapse during the first-line protocol typically requires the use of alternative drugs (meaning drugs not included in the first protocol), while a relapse following completion of the first-line protocol leaves the possibility for including drugs used in the original protocol. Rescue protocols typically result in lower response rates, shorter durations of response (2−3 months), and tend to show more toxicity than first-line protocols.

8.1.4. Additional remarks on the chemotherapeutic treatment of canine lymphoma

8.1.4.1. T-cell lymphoma and stage V disease. Most studies show that T-cell and stage V lymphomas carry a poorer prognosis and as a result alternative protocols have been suggested. For T-cell lymphomas it has been suggested that alkylating-agents-based protocols like L-asparaginase-MOPP (Brodsky et al. 2009) might be superior to a classic CHOP-based protocol. However, a recent study reported the use of a regular CHOP protocol in dogs with multicentric T-cell lymphoma and obtained treatment results comparable to those for B-cell lymphomas (Rebhun et al. 2011). For dogs with stage V disease it has been suggested to prolong the maintenance phase or include other drugs. Adding cytosine arabinoside to a CHOP-based protocol appears to improve survival in stage V dogs (Marconato et al. 2008).

8.1.4.2. Low-grade lymphomas. Since chemotherapeutic agents predominantly affect actively replicating cells, it can be argued that chemotherapy should be used cautiously in slowly proliferating, also referred to as low-grade or indolent, lymphomas. In human medicine, most indolent lymphomas, which include follicular lymphoma, chronic lymphocytic leukemia/small

lymphocytic lymphoma, and marginal zone lymphoma, are initially not treated and typically a 'watchful waiting' strategy is recommended. Only in advanced stages of the disease, defined as the presence of systemic signs, bulky disease, and/or bone marrow depression, treatment is recommended. Based on this strategy in humans, it would make sense that asymptomatic dogs with indolent lymphomas would only be monitored. Recently, some case series have demonstrated that dogs with low-grade lymphomas have a good long-term prognosis and that the use CHOP-based protocols offers no survival benefit (Valli et al. 2006; Stefanello et al. 2011; Flood-Knapik et al. 2013; O'Brien et al. 2013; Seelig et al. 2014). It is, therefore, recommended that indolent nodal lymphomas should be monitored and either not be treated or treated with a low-intensity protocol like chlorambucil and prednisolone, while for the splenic variant it is advised to restrict treatment to splenectomy.

8.1.4.3. Dogs with severe bone marrow, kidney, or liver involvement and tumor lysis syndrome. Chemotherapeutic treatment of dogs with neutropenia due to bone marrow involvement (stage V) or impaired liver or kidney function and bulky disease remains challenging. On the one hand, chemotherapy is the only way to restore organ function; while on the other hand, these patients are at high risk for developing drug-related toxicity (sepsis) and tumor lysis syndrome (Page et al. 1986; Altman 2001; Vickery and Thamm 2007) due to the reduced capability of metabolizing chemotherapeutic agents and excreting waste products. Tumor lysis syndrome is characterized by elevated serum levels of uric acid, phosphate, potassium, and urea combined with low serum calcium levels (Piek and Teske 1996; Altman 2001), and can lead to nausea, vomiting, acute renal failure, seizures, and cardiac arrhythmias. For patients at high risk of developing tumor lysis syndrome, it is advised to initiate forced diuresis with intravenous fluid therapy and use drugs that will not cause overwhelming cell death or whose metabolism is independent of liver and/or kidney function. Possible drugs to consider would include pretreatment with glucocorticoids or start the protocol with L-asparaginase or vincristine. An alternative option is the use of allopurinol or rasburicase (Cairo et al. 2010) both of which will prevent the buildup of excessive uric acid levels.

8.1.4.4. Central nervous system lymphoma. Treating central nervous system lymphoma comes with the additional problem of the blood−brain barrier (BBB) that limits the penetration of cytostatic drugs into the brain and spinal cord. There are two ways of circumventing this problem, either to use drugs that are able to pass the BBB like L-asparaginase, cytosine arabinoside (Scott-Moncrieff et al. 1991), and nitrosurea

compounds (Dimski and Cook 1990; Jeffery and Brearley 1993) or administer the drug within the subarachnoid space (intrathecal cytosine arabinoside) (Couto et al. 1984).

8.1.4.5. *Drug resistance in canine lymphoma.* The efficacy of chemotherapy is limited by the onset of drug resistance (DR) and due to the limited alternative treatment options for cL, the development of DR has a grave impact on prognosis. DR can have many causes (Lage 2008), but drug transporters of the ATP-Binding Cassette superfamily, including P-gp (ABCB1), MRP1 (ABCC1), and BCRP (ABCG2), are thought to play an important role (Bergman et al. 1996; Lee et al. 1996; Page et al. 2000; Tashbaeva et al. 2007; Mealey et al. 2008; Honscha et al. 2009; Hifumi et al. 2010). A recent prospective study showed that although ABC-transporter mRNA expression is common in cL, it is unlikely to be the sole cause for DR (Zandvliet et al. 2015). Intrinsic DR was more common in T-cell than B-cell lymphoma, and while DR in T-cell lymphoma was associated with increased ABCG2 expression, acquired DR in B-cell lymphomas tended to be associated with ABCB1 overexpression.

Based on these findings, there are two therapeutic options available, either reversal of DR using P-gp and BCRP inhibitors or use cytotoxic drugs that are neither P-gp nor BCRP substrates. P-gp inhibitors that might be useful in the treatment of DR cL include PSC833 (Valspodar®) and the tyrosine-kinase inhibitor masitinib ((Zandvliet et al. 2013b, Zandvliet et al. 2014). Although the use of Valspodar® in DR lymphoma sounds promising, inclusion of PSC833 in a first-line CHOP-based protocol offered no treatment benefit (Ito et al. 2015b). Drugs that are not typical substrates for the ABC transporters ABCB1 and ABCG2 include alkylating agents and L-asparaginase, drugs that are typically used in the various rescue protocols.

8.2. Radiotherapy

Although (neoplastic) lymphoid cells are radiosensitive, lymphoma typically presents as a systemic disease and, as a result, radiotherapy plays a limited role in its management. Nevertheless, the use of radiotherapy has been reported for both localized forms and multicentric lymphoma, both in the setting of a monotherapy as well as an adjuvant therapy.

The successful use of radiotherapy for localized cL has been reported in an adjuvant setting to surgery and/or chemotherapy for mediastinal (LaRue et al. 1995) and urinary bladder (Kessler et al. 2008) lymphoma, and as a monotherapy for oral mucocutaneous cL (Berlato et al. 2012). Radiotherapy has also been used as a rescue therapy in dogs with DR multicentric cL and in these cases all peripheral lymph nodes were irradiated (6 × 2 Gy, 3x/week) with all dogs achieving a complete remission and a median survival of 143 days (Hahn 2002).

Treating multicentric cL with radiotherapy requires radiating the whole body and this can be done in a single session of whole-body irradiation (WBI) or two separate sessions of half-body irradiation (HBI). HBI has less side effects (bone marrow, gastrointestinal) than WBI and is therefore preferred by most clinicians. Although a monotherapy with radiotherapy (2x HBI with 7Gy 28 days apart) has been described for treating multicentric cL, the reported results were poor and adverse events common and particularly severe in dogs with advanced stage of disease (Laing et al. 1989).

Radiotherapy is more commonly used as an adjuvant therapy to systemic chemotherapy and can be prescribed as TBI or HBI. TBI carries the risk of severe bone marrow depression and therefore needs to be combined with (autologous) bone marrow or peripheral blood stem cell transplantation. Bone marrow transplantation in the dog was already performed in 1979 (Weiden et al. 1979) and although initial reports showed promising results, treatment-related morbidity and mortality were high (Deeg et al. 1985; Appelbaum et al. 1986). Although a more recent report showed less treatment-related morbidity and mortality (Willcox et al. 2012), TBI has been gradually replaced by (two sessions of) HBI. HBI can be performed either during or at the end of the chemotherapy protocol and radiation can be administered at either a high-dose rate (regular-dose rate for conventional radiotherapy ±400 cGy/min) or low-dose rate (10cGy/min). The high-dose rate HBI protocol consists of 8 Gy (2 × 4 Gy given on two consecutive days) to the cranial half of the body and was repeated 3−4 weeks later for the caudal half of the body. This protocol has been used both within (Gustafson et al. 2004) and following completion (Williams et al. 2004) of a CHOP-based chemotherapy protocol and resulted in a median duration of first remission of 455 days and 311 days, respectively, and a median OST of 560 and 486 days, respectively. An alternative approach has been to use low-dose rate HBI (10 cGy/min; two fractions of 6 Gy on two consecutive days two weeks apart) within a CHOP-based chemotherapy protocol and this led to a first duration of remission of 410−455 days and OST of 560−684 days with acceptable toxicity (Lurie et al. 2009).

8.3. Immunotherapy

Although immunotherapy plays a major role in the treatment of many human B-cell malignancies, its role in cL is still limited. A monoclonal antibody targeting the CD20 receptor (Rituximab®) has significantly improved disease-free period and overall survival in human B-cell NHL. Although immunohistochemistry demonstrated the presence of CD20 in cL (Jubala et al. 2005; Kano et al. 2005), it failed to bind Rituximab®

(Impellizeri et al. 2006) and new anti-canine CD20 monoclonal antibodies are being developed (Ito et al. 2015a). The use of other antibodies has been reported and includes the use of a murine anti-canine lymphoma monoclonal antibody (MAb-231) that showed both *in vitro* (Rosales et al. 1988) and *in vivo* (Steplewski et al. 1990) activities in cL and the murine anti-human leukocyte antigen-DR monoclonal antibody (L243) that was used in dogs with cL but was only able to temporarily stabilize disease progression (Stein et al. 2011).

In the literature various types of vaccination strategies have been reported for the treatment of cL. In the earliest studies, killed lymphoma cell extracts were combined with Freund's adjuvans and although initial reports showed a treatment benefit (Crow et al. 1977), this was later attributed to the use of the Freund's adjuvans (Weller et al. 1980). Intralymphatic administration of a killed autologous tumor vaccine following induction with chemotherapy was reported by Jeglum et al. (1986, 1988, 1989), but the reported results were inconsistent and survival benefit could only be demonstrated for subsets of patients.

A DNA vaccine targeting canine telomerase reverse transcriptase (cTERT) was able to induce an immune response against telomerase in dogs with multicentric cL (Peruzzi et al. 2010) and the combined use of the vaccine and chemotherapy (COP protocol) resulted in both a lasting immune response, as well as an increase in survival without adverse events in dogs with B-cell lymphoma (Gavazza et al. 2013). The use of an autologous vaccine consisting of hydroxyapatite ceramic powder with autologous heat shock proteins purified from a neoplastic lymph node proved effective in prolonging disease control without increasing treatment toxicity (Marconato et al. 2014).

The use of autologous CD40-activated B-cells loaded with total RNA from autologous lymphoma cells following induction of a complete response with chemotherapy resulted in a functional tumor-specific T-cell response *in vivo*, but there was no improvement in treatment results following the first-line treatment, but only improved rescue therapy results (Sorenmo et al. 2011). The use of adoptive immunotherapy using non-specific autologous T-cells was proven feasible and effective in increasing the length of first remission and overall survival in dogs with multicentric cL (O'Connor et al. 2012).

8.4. Miscellaneous therapies

Retinoic acid receptor (RAR) and retinoid X receptor (RXR) expression are commonly and exclusively expressed in the neoplastic lymphoblasts in both cutaneous (de Mello Souza et al. 2010) and multicentric cL (de Mello Souza et al. 2014). Their role in cL is not understood, but offers potential applications for both diagnosis and treatment. A small study in dogs with cutaneous cL showed a 42% (6/14) remission rate using isotretinoin and etretinate, but more studies are necessary before this treatment can be recommended (White et al. 1993).

Targeted therapy is expected to find its place in cL treatment as in many other cancers and potential drug-able targets include the anaplastic lymphoma kinase (Gingrich et al. 2012) and NF-κB. NF-κB activity can be targeted using the NF-κB inhibitor Bortezomib® (Kojima et al. 2013) or the NF-κB essential modulator (NEMO)-binding domain peptide (Gaurnier-Hausser et al. 2011). The use of NEMO-binding domain peptide has been reported in dogs with multicentric B-cell lymphoma and was shown to successfully inhibit NF-κB activity, reduce both the mitotic index and cyclin D expression in most dogs without significant toxicity (Habineza Ndikuyeze et al. 2014). Canine epitheliotropic cutaneous T-cell lymphoma is typically treated with the chemotherapeutic agent CCNU (Risbon et al. 2006; Williams et al. 2006), but the tyrosine kinase inhibitor masitinib appears a potential alternative therapy (Holtermann et al. 2015).

Other therapies reported include the combined use of hyperthermia with chemotherapy, which failed to improve treatment outcome (Larue et al. 1999), and the potential for viral lympholytic therapy with canine distemper virus based on *in vitro* studies that demonstrated the capacity of this virus to infect lymphoid cells and induce apoptosis (Suter et al. 2005).

9. Prognosis

Many prognostic factors have been evaluated in the dog and include clinical data, pretreatment clinical pathology results, histology, immunophenotype, grade, proliferation markers, molecular prognosticators, and biomarkers. In human high-grade NHL, disease prognosis is successfully stratified using the International Prognostic Index (IPI) that includes the factors age, stage, elevated serum LDH activity, performance status, and involvement of extranodal sites, but a similar index has not yet been developed for high-grade cL.

9.1. Clinical data

Most literature on cL deals with intermediate- to high-grade multicentric lymphoma and reports that sex, weight, WHO stage, and substage are prognostic for remission and survival. Female, small-breed dogs with stages I−IV and substage *a* have a more favorable prognosis than male, large-breed, stage V, and substage *b* dogs (Greenlee et al. 1990; Hahn et al. 1992; Keller et al. 1993; Kiupel et al. 1999; Dobson et al. 2001; Garrett et al. 2002).

In general, extranodal lymphomas, including GI (Frank et al. 2007; Rassnick et al. 2009), hepatic (Dank

et al. 2011; Keller et al. 2013), mediastinal (Rosenberg, Matus, Patnaik 1991; Starrak et al. 1997), cutaneous (Fontaine et al. 2010), and renal lymphoma, have a poorer prognosis than the multicentric form. Despite this generalization, it has to be realized that within all of these groups, subsets of dogs may perform better. While, for instance, small intestinal lymphoma has a median survival of 77 days (Rassnick et al. 2009), most likely due to intrinsic DR (Frank et al. 2007), rectal lymphoma has a median survival of greater than 1700 days (Van den Steen et al. 2012).

Treatment with glucocorticoids prior to starting chemotherapy reduces the response rate to chemotherapy (Price et al. 1991; Teske et al. 1994; Marconato et al. 2011). Failure to respond to therapy (no complete response) at the start of therapy or following relapse negatively affects treatment outcome. In all these situations, treatment failure is thought to result from drug resistance. Although pretreatment P-gp expression was found to be prognostic in older studies (Bergman et al. 1996; Lee et al. 1996), more recent studies were not able to confirm this (Dhaliwal et al. 2013; Gramer et al. 2013; Zandvliet et al. 2015).

9.2. Pretreatment clinical pathology results

In contrast to human NHL, absolute lymphocyte count and neutrophil/lymphocyte ratio (>3.5) were not predictive for progression-free survival in the dog (Mutz et al. 2013), but increased neutrophil and monocyte counts correlated with monocyte chemotactic protein-1 (MCP-1) overexpression and a shorter disease-free interval (Perry et al. 2011). Hypercalcemia is a poor prognostic indicator (Marconato et al. 2011), but also associated with the T-cell immunophenotype (Greenlee et al. 1990; Teske et al. 1994) and it has been shown that the presence of hypercalcemia in T-cell lymphomas has no further negative effect on response to treatment or survival (Rebhun et al. 2011). Serum LDH (lactate dehydrogenase) (Greenlee et al. 1990; von Euler et al. 2006) or ALP activities (Wiedemann et al. 2005) were not predictive for treatment response.

9.3. Histology, immunophenotype, grade, and proliferation indices

In general, T-cell lymphomas have shorter remission and survival times than B-cell lymphomas (Greenlee et al. 1990; Teske et al. 1994; Ruslander et al. 1997; Ponce et al. 2004; Valli et al. 2013). Most T-cell lymphomas are CD4+ CD45+ high-grade lymphomas, histologically characterized as peripheral T-cell lymphoma NOS or lymphoblastic lymphoma (Table 4), with an aggressive disease course (median survival 159 days). A minority of T-cell lymphomas is characterized as CD4+ CD45− with high-class II MHC expression, a combination diagnostic for T-zone lymphoma (Avery

et al. 2014). T-zone lymphoma is a low-grade lymphoma typically diagnosed in older (median 10 years) golden retrievers with lymphadenopathy and peripheral lymphocytosis and carries a good prognosis (median survival 637 days) (Seelig et al. 2014).

Proliferative indices include mitotic index, PCNA, Ki-67, and agryrophilic nucleolar organizer regions (AgNOR), of which Ki-67 and AgNOR can be assessed in both histological and cytological samples (Vajdovich et al. 2004). Ki-67, PCNA, and AgNOR expression is higher in cL than in benign lymphoid proliferations (Hipple et al. 2003; Bauer et al. 2007). Furthermore, AgNOR and Ki-67 expression levels correlated with grade (Fournel-Fleury et al. 1997a; Kiupel et al. 1998; Poggi et al. 2015) and proved of prognostic value in contrast to mitotic index and PCNA expression (Vail et al. 1996; Kiupel et al. 1998; Valli et al. 2013).

9.5. Molecular biology and other prognosticators

Using gene expression profiling (DNA microarrays), DLBCL, the most common form of human NHL, could be subdivided into a germinal center B-cell-like (GCB) and a post-germinal center or activated B-cell-like (ABC) subtype with the former subtype having a longer overall survival than the latter (Alizadeh et al. 2000). A similar differentiation can be made using immunohistochemistry for the detection of CD10, Bcl-6, MUM-1/RF4, FOXP1, Cyclin D2, Bcl-2, GCET1, and MTA3 (Hans or Choi algorithm) (Hans et al. 2004; Choi et al. 2009). In the dog, genome-wide gene expression of cL cases showed three distinct molecular subgroups: high-grade T-cell, low-grade T-cell, and B-cell lymphoma (both high and low grades) (Frantz et al. 2013). This subdivision also correlated with prognosis (survival) and could be accurately predicted based on the expression of only four genes (CD28, abca5, CCDC3, and SMOC2) (Frantz et al. 2013). Gene expression profiling of canine diffuse large B-cell lymphoma showed similarities with hDLBCL and suggested the existence of GCB- and ABC-like subsets. Immunohistochemistry proved less useful in dogs than in humans since dogs rarely express Bcl-6 and MUM-1/RF4 (Richards et al. 2013).

Other reported prognostic factors include trisomy of dog chromosome 13 (Hahn et al. 1994), high-class II MHC expression (Rao et al. 2011), the absence of MRD in the blood (Gentilini et al. 2013; Sato et al. 2013) and VH1-44 (immunoglobulin heavy-chain variable region) gene expression in B-cell lymphoma (Chen et al. 2014), all of which were associated with a better prognosis. The detection of p53 (Dhaliwal et al. 2013) and p16 (mRNA) expression (Fujiwara-Igarashi et al. 2014) correlated with a shorter overall survival time.

Survivin, a member of the inhibitor of apoptosis protein (IAP) family, inhibits caspases and as a result apoptosis. Survivin is commonly expressed in a variety of

human and canine cancers including cL (Wimmershoff et al. 2010) and increased survivin expression correlated with a shorter median disease-free period (Rebhun et al. 2008).

Pretreatment PARR results (Lana et al. 2006b), expression of CD34, CD21, and DC5 (Rao et al. 2011), expression of angiogenic factors (VEGF, VEGFR-1, VEGFR-2), and micro-vessel density (Wolfesberger et al. 2012) were of prognostic value.

9.5. Biomarkers

Of all reported biomarkers so far, only serum TK1 levels (von Euler et al. 2004) were prognostic, although serum C-reactive protein and haptoglobin levels combined with a diagnostic algorithm might prove of use (Alexandrakis et al. 2014). Alpha 1-acid glycoprotein (Hahn et al. 1999b) and glutathione-S-transferase plasma levels (Hahn et al. 1999a) were found to be of no prognostic value, although both increased prior to relapse, and the data on alpha-fetoprotein levels are conflicting (Hahn and Richardson 1995; Lechowski et al. 2002) and its use is therefore not recommended.

10. Future goals and challenges

Although our knowledge on the genetics, molecular biology, and diagnosis of cL has grown substantially over the past 25 years, this has had little effect on treatment and has only marginally improved prognosis.

Chemotherapy still remains the mainstay for the treatment of cL and it appears that we have reached a plateau in what this treatment modality has to offer. More elaborate and more intense chemotherapy protocols increase toxicity, but do not improve treatment outcome. This results partly from the onset of drug resistance, but in part also from the lack of new (classes of) chemotherapeutic agents. A potentially major step forward in the treatment of cL with chemotherapy would be the possibility to prevent, delay, or circumvent drug resistance, and in order to do so we need to improve our knowledge of DR to cytostatic agents in general and cL in particular.

Since local therapies including surgery and radiotherapy remain to be of limited value, and new classes of cytostatic drugs are not available, we need to focus on other systemic treatment modalities including immunotherapy and targeted therapy. Especially for this last form of treatment, a detailed understanding of the molecular pathways involved in lymphomagenesis is adamant and requires a thorough characterization of each of the specific subtypes of cL.

Acknowledgments

Disclosure statement

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