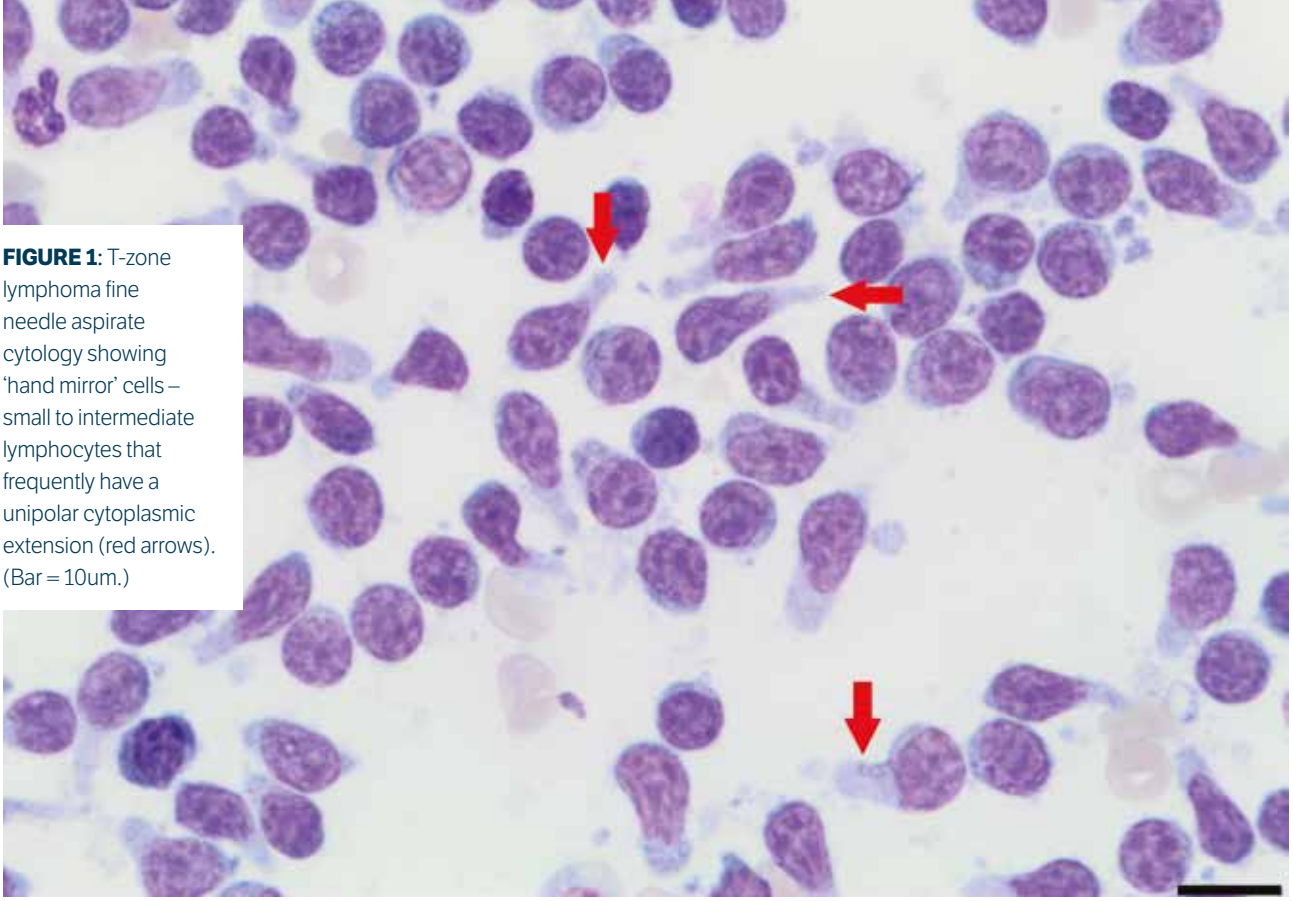

FIGURE 1: T-zone lymphoma fine needle aspirate cytology showing 'hand mirror' cells – small to intermediate lymphocytes that frequently have a unipolar cytoplasmic extension (red arrows). (Bar = 10um.)

Canine indolent lymphoma – *why do we need to know about it?*

Clinical and Anatomic Veterinary Pathologist **Michelle Lepherd** of Gribbles Veterinary Christchurch highlights a potentially underdiagnosed subset of lymphomas.

WHILE THE MOST common types of lymphoma in dogs are of the high-grade, large cell, B- or T-cell type that most of us would be familiar with, there is a significant subset of indolent lymphomas that may account for up to 30% of canine lymphoma cases and are probably underdiagnosed (Flood-Knapik et al., 2013; Valli et al., 2013). In terms of survival and prognosis, it may be just as important to differentiate aggressive versus indolent lymphoma, in addition to B- versus T-cell lymphoma, as low-grade, indolent lymphomas can have a long survival time and often require conservative or no therapy.

Canine lymphoma is a heterogeneous disease with highly variable clinical presentation, progression, and prognosis. In many instances, a generic diagnosis of lymphoma is made based on cell morphology only, without assessment of architecture or immunophenotype. Specific therapy based on a specific subset of lymphoma type is therefore largely lacking in the veterinary world, compared with the tailored treatment regimens implemented in human oncology.

The most common indolent lymphomas include T-cell lymphoma and the B-cell indolent lymphomas, including marginal cell lymphoma, mantle cell lymphoma, and follicular lymphoma (Flood-Knapik et al., 2013; Valli et al., 2006). Other, less common, indolent lymphomas in dogs include small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and T-cell rich B-cell lymphoma.

A dog with an indolent lymphoma may present with one or more enlarged lymph nodes or a solitary splenic nodule (found on palpation, ultrasound, or subsequent to haemoabdomen), and is, more often than not, clinically well. In some dogs, the lymph nodes may have been enlarged for several months or years prior to presentation (Valli et al., 2006).

Indolent lymphomas are typically composed of small- to intermediate-sized lymphocytes that have a low mitotic rate.

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They can be mistaken for lymphoid hyperplasia or a reactive lymph node on fine needle aspirate (FNA) cytology, as they lack the significant numbers of large lymphocytes that help to cytologically diagnose the more common large cell lymphomas.

While the clued-up pathologist can often get a suspicion of indolent lymphoma from cytology findings and detailed clinical history, histopathology is essential for confirmation. Whole node or large wedge-shaped biopsies that incorporate capsule, cortex and medulla are required, as most indolent lymphomas have a characteristic pattern of follicular expansion and effacement.

Tru-cut and narrow core biopsies are often unrewarding, as they don't include enough architecture for diagnosis. In many cases, routine histopathology of an adequately sized biopsy will be sufficient to diagnose the subtypes of indolent lymphoma. However, in more advanced cases, where there is greater effacement of architecture and obscure residual follicles, immunophenotyping for B- and T-cell markers can be enormously helpful in recognising the follicle-related heritage and fading follicles that characterise most indolent lymphomas. The detection of clonality is a useful adjunct to histology and immunohistochemistry, particularly in those cases with an ambiguous morphology and immunophenotype.

T-zone lymphoma (TZL) is the most common type of indolent lymphoma and, as the name suggests, is of T-cell origin, developing as an expansion of the paracortical areas between fading follicles.

A clue to diagnosis can often be seen on FNA of affected lymph nodes, due to the presence of large numbers of small to intermediate lymphocytes that frequently have a unipolar cytoplasmic extension (hand mirror cells – Figure 1).

Dogs with TZL often have generalised lymphadenopathy, and therapy does not appear to positively influence survival or quality of life (Valli et al., 2006; Valli et al., 2013).

The second most common type of indolent lymphoma is marginal zone lymphoma (MZL), which is of B-cell origin, and occurs in either lymph nodes or, more commonly, the spleen. It is characterised by coalescing perifollicular proliferation of marginal cells and paracortical atrophy. Splenic MZL often has a good response to splenectomy alone (Valli et al., 2006).

WHILE THE CLUED-UP PATHOLOGIST CAN OFTEN GET A SUSPICION OF INDOLENT LYMPHOMA FROM CYTOLOGY FINDINGS AND DETAILED **CLINICAL HISTORY, HISTOPATHOLOGY IS ESSENTIAL FOR CONFIRMATION.**

Interestingly, 10-50% of dogs with indolent lymphoma also have demodicosis (Flood-Knapik et al., 2013; Mizutani et al., 2016). *Demodex* spp. infestation is usually associated with immunosuppression and the presence of indolent lymphoma may predispose to immune dysregulation and subsequent demodicosis. Also, demodicosis itself may cause further immunosuppression. Further work-up for lymphoma may be warranted in older dogs with generalised demodicosis, and should include lymph node biopsy, rather than just FNA, to ensure indolent lymphoma can be detected.

Median lymphoma-specific survival time for indolent lymphoma has been reported to be as long as 4.4 years and the median overall survival time (OST) as 21.2 months, and is longest for TZL (median OST of 33.5 months) (Flood-Knapik et al., 2013). Dogs with solitary splenic nodules are reported to do well with splenectomy alone (Flood-Knapik et al., 2013; Valli et al., 2006).

In fact, many dogs can do well without treatment, and 'watchful waiting' may be a reasonable approach, particularly in the earlier phases of disease. However, it appears that some indolent B-cell lymphomas can behave like, or transform into, high-grade lymphomas. There is no established consensus about when to treat dogs with indolent lymphoma. For asymptomatic TZL, Moore (2016) suggests watchful waiting with careful monitoring of peripheral nodes and haematology.

Further therapy should be considered if dogs develop clinical signs, have rapid progression (defined as a tumour doubling time of less than six months), a circulating lymphocyte count greater than 9.2×10^9/L, multiple sites of lymphoma larger than 3cm in diameter or a single site greater than 7cm in diameter, development of myelosuppression due to myelophthisis, or organ dysfunction due to infiltration. Chemotherapy for indolent lymphoma ranges from prednisone alone, combination prednisone and chlorambucil, or CHOP-based chemotherapy protocols, similar to those used for aggressive lymphoma (Flood-Knapik et al., 2013).

In the future, better characterisation and more precise diagnoses of lymphoma, alongside the documentation of responses to specific treatments, will hopefully allow for more accurate prognostications and lymphoma-specific therapy. VS

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