HISTOLOGICAL CLASSIFICATION AND MOLECULAR CHARACTERIZATION OF FELINE HODGKIN-LIKE LYMPHOMAS (HLL)

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INTRODUCTION

Hodgkin lymphoma (HL) comprises a group of lymphoid neoplasms deriving from germinal center or post-germinal B-cells in humans.[1] Hodgkin-like lymphoma (HLL) has been sporadically described in cats.[2] In humans, HL is a primary nodal tumor with diverse architectural growth patterns and heterogeneous cell components that consist of variable proportions of reactive lymphoid cells and large, mononucleated (Hodgkin) and/or bi- to multinucleated giant (Reed-Sternberg), neoplastic cells.[1] Morphology enables the distinction of classical HL variants (nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted HL) and nodular lymphocyte-predominant HL.[1] Differentiation of human HL from Non-Hodgkin lymphoma (NHL) is relevant because HL bears a better prognosis with the different HL types have diverse clinical behaviors and responses to therapy.[1]

AIMS

To describe morphological, phenotypical, and molecular features of feline HLL useful for the differentiation with mixed non-HLL.

MATERIALS

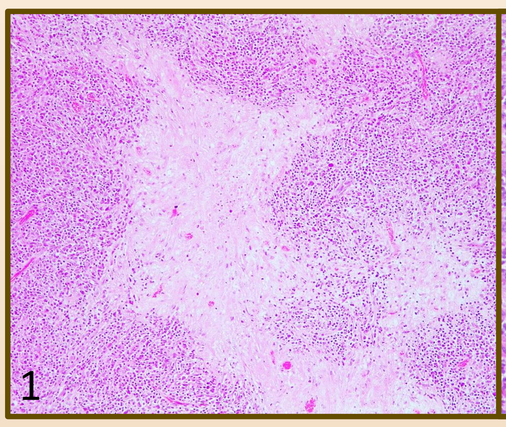
A total of 21 cases of feline primary nodal lymphoma with mixed morphology and a putative diagnosis of HLL were collected from 2006-2023 by multiple institutions. Biopsy samples or complete lymph nodes were fixed and routinely processed for histology, immunohistochemistry (anti-CD3, -CD20, -CD30, -PAX-5), and clonality assessments.

RESULTS

Of 21 lymphomas, 12/21 were confirmed as HLL and were observed in 9/12 DSH and 3/12 Maine coon cats with a F/M ratio of 1. Non-HLL lymphomas were diagnosed in 9/12 cases all in DHS cats with a F/M ratio of 0.8. All cats presented with only one enlarged lymph node. Pathological findings and definitive diagnoses of HLL lymphoma types are listed in Table 1.

- **Histology of feline HLL**

Lymph node architecture was effaced in all cases. Most consistent microscopical findings included extensive colliquative necrosis (Fig. 1), predominance of reactive lymphocytes admixed with lesser numbers of large neoplastic cells (Fig. 2). Reed-Sternberg and Hodgkin cells were always observed (Fig. 3, 4), while Popcorn cells were present in 4/12 cases (Fig. 5)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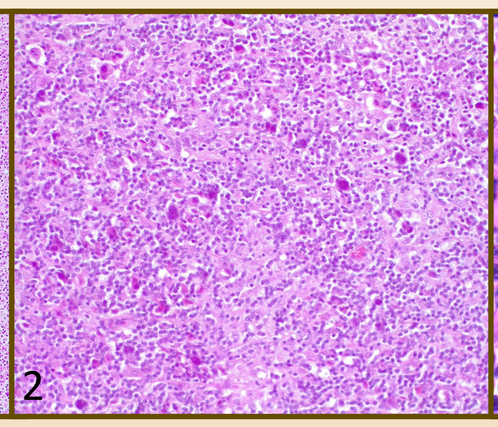
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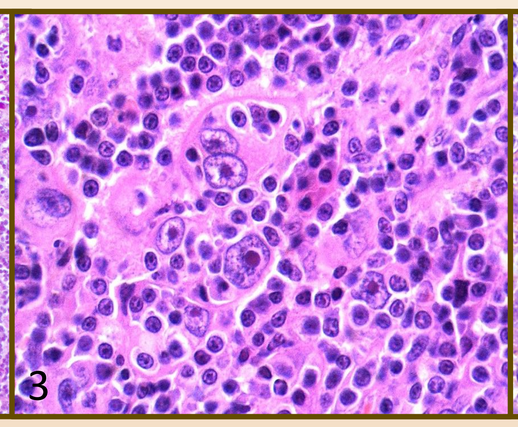
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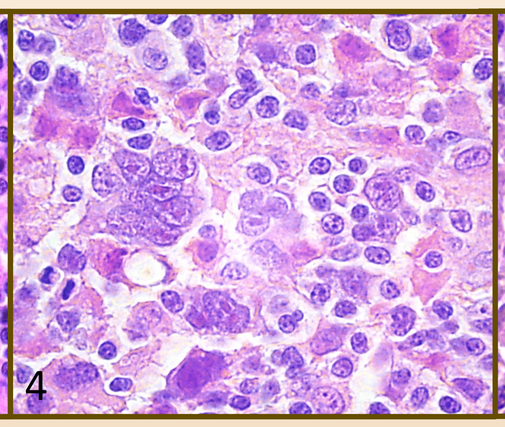
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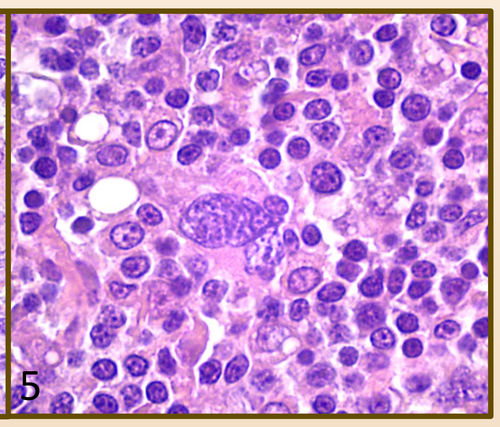
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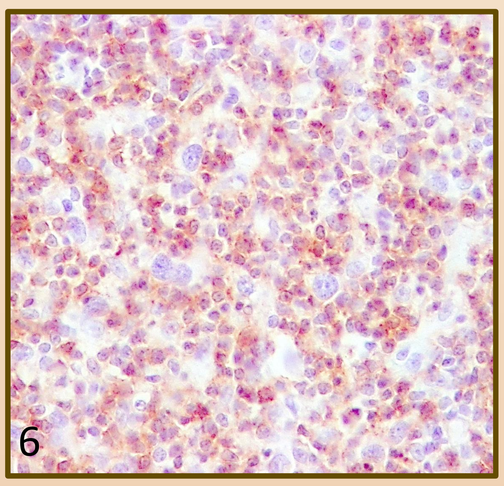
- **Immunohistochemistry and Clonality**

In all HLL, neoplastic cells were CD3 negative (Fig. 6), consistently expressed CD30 (Fig. 7), and expressed CD20 and PAX-5 variably (Fig. 8, 9). Most NHL were CD30 negative, while 4/9 expressed CD30. Clonal IGH rearrangement was detected in 8/12 HLL and 8/9 NHL. Clonal TCR rearrangement was detected in 3 HLL with a B cell phenotype.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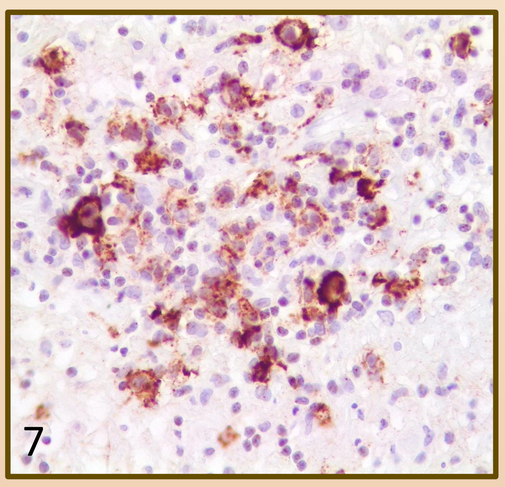
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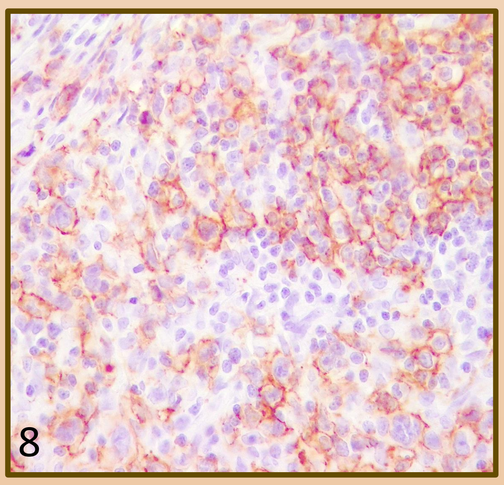
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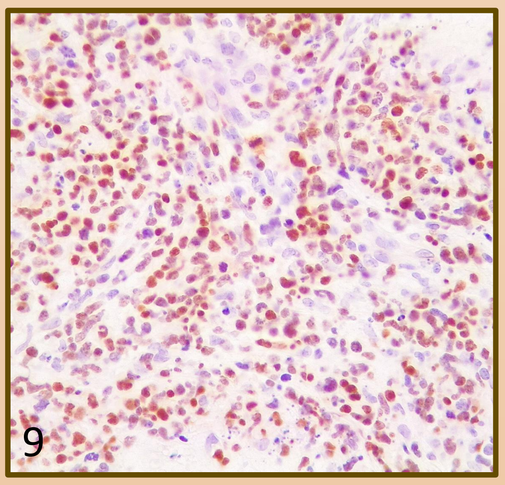
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Cat	Growth pattern	% Neoplastic cells	% necrosis	RSC	HC	Pop Corn	Large Neoplastic cells				Reactive lymphocytes	IGH	TRG	Diagnosis
							CD30	CD20	PAX-5	CD3				
1	Diffuse	30%	15%	+	+++	NP	30%	-	-	-	30% B 70% T	-	-	Lymphocyte-rich HLL
2	Diffuse	20%	NP	+	+	NP	NA	NA	NA	NA	NA	NA	NA	Lymphocyte-rich HLL
3	Nodular	50%	40%	+++	+	NP	100%	90%	20%	-	30% B; 70% T	-	+	Nodular sclerosis HLL
4	Diffuse	30%	5%	++	++	NP	40%	-	-	-	20% B; 80% T	+	-	Lymphocyte-rich HLL
5	Diffuse	30%	NP	++	+	NP	100%	50%	40%	-	30% B; 70% T	+	-	Lymphocyte-rich HLL
6	Diffuse	50%	NP	++	+++	++	80%	70%	70%	-	70% B; 30% T	-	+	Classic HLL
7	Diffuse	70%	40%	++	+++	NP	100%	70%	60%	-	70% B; 30% T	+	-	Mixed cellularity HLL in B cell transformation
8	Diffuse	20%	10%	++	++	+	30%	10%	10%	-	15% B; 85% T	+	-	Lymphocyte-rich HLL
9	Diffuse	50%	NP	+	+++	NP	20%	70%	60%	-	50% B; 50% T	+	-	Mixed cellularity HLL in B cell transformation
10	Diffuse	30%	30%	+++	+++	+	100%	80%	40%	-	20% B; 80% T	-	+	Lymphocyte-rich HLL
11	Nodular	40%	30%	+	++	NP	70%	70%	20%	-	60% B; 40% T	+	-	Nodular sclerosis HLL
12	Nodular	40%	30%	+++	+++	+	100%	80%	100%	-	10% B; 90% T	+	-	Classic HLL

Table 1. Legends: NP: Not Present; NA: Not Available; -: Negative

DISCUSSION

Differentiation between feline HLL and non-HLL with mixed morphology (e.g. T cell rich B cell lymphoma) proved challenging on sole morphological grounds. One finding uncommon in non-Hodgkin lymphomas was the extensive necrosis that together with the mixed cellularity and presence of Hodgkin cells can be considered useful clues to HLL diagnosis in cats. There was no single technique able to discriminate HLL and NHL in all cases. Most useful diagnostic clues included lymph nodal effacement, extensive areas of colliquative necrosis, prevalence of reactive T cells with admixed large neoplastic Reed-Sternberg and Hodgkin cells expressing CD30. Most cases expressed CD20 and/or PAX-5 and had clonal IGH rearrangement confirming a B cell origin of HLL in cats. Despite B cell marker expression, 3 cases had TCRG rearrangement attributed to a lineage infidelity. Only the use of multiple techniques together with the clinical presentations allow for a definitive diagnosis of feline HLL. More cases with available follow up are needed to assess the clinical behavior of HLL in cats.

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