

Aggressive behaviour of Hodgkin's-like lymphoma in a domestic ferret

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Abstract: A 3-year-old castrated male ferret was suspected to have lymphoma based on a markedly enlarged mesenteric lymph node. Hodgkin's-like lymphoma (HLL) was suspected because numerous Reed-Sternberg-like cells were observed in the fine-needle aspiration biopsy of the mesenteric lymph node. In the post-mortem histopathology, neoplastic cells were invasively proliferated not only in the mesenteric lymph nodes, but also in the liver and spleen. Immunohistochemically, most neoplastic cells were positive for vimentin and BLA-36, weakly positive for CD20, and negative for Pax5, CD79a, CD3, CD45, and Iba-1, demonstrating similarity to human Hodgkin's lymphoma (HL). In addition, a prominent programmed cell death protein 1 (PD-1) expression was observed at the sites showing malignant tumour proliferation. HLL in non-human beings can be morphologically and immunophenotypically similar to human HL, but the prognosis and clinical outcome may differ. This is the first study analysing the PD-1 expression in a ferret, suggesting that PD-1 can be a novel diagnostic and prognostic factor in a similar manner to humans.

Keywords: cytology; histopathology; immunohistochemistry; programmed cell death protein 1; Reed-Sternberg cell

The classification of human Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) is constantly being updated. According to the World Health Organization/Revised European-American Lymphoma classification, HL is classified into two groups: classical HL (CHL) and nodular lymphocyte predominance HL (NLPHL). CHL can be further classified into four subtypes: nodular sclerosis, lymphocyte-rich, mixed cellularity, and lymphocyte-depleted CHL (Ammersbach

et al. 2008; Swerdlow et al. 2016; Matsumoto et al. 2017). In contrast, HL in small animals is not well characterised; although Hodgkin's-like lymphoma (HLL) was described as early as the 1990s, only a few HLL cases in dogs, cats, and ferrets have been documented (Maeda et al. 1993; Blomme et al. 1999; Walton and Hendrick 2001; Matsumoto et al. 2017). Human HL arises from B-cells in the germinal centre and tends to progress more slowly and be less aggressive than NHL (Josting et al. 2000). HL may

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occur in a single lymph node or a group of lymph nodes, while extranodal involvement is uncommon in the early stages. A study of 20 feline HLL cases demonstrated that feline HLL may also be less aggressive than NHL as described in humans (Walton and Hendrick 2001).

The clinical prognosis and characteristics of the disease vary according to the histological subtype of the HL and NHL; therefore, an accurate diagnosis is important for human lymphoma treatment. Human HL is considered relatively benign and curable when appropriate treatments are administered, although the prognosis can differ depending on the stage at diagnosis (Josting et al. 2000). HLL is rarely diagnosed in animals and shares the same diagnostic criteria as human HL. However, the immunophenotypes and clinical features can differ, and since only a few cases have been reported, the diagnoses and features of HLL should be carefully interpreted (Blomme et al. 1999).

In domestic ferrets (*Mustela putorius furo*), lymphoma is the most common malignancy and the third most common type of neoplasm (Hammer et al. 2007; Williams and Wyre 2020). The multicentric form is the most common, which affects older ferrets more frequently (over 3 years of age). Clinical signs are usually absent in the early stages, and the visceral organs, including the liver, spleen, and kidney, can be affected in later stages (Fox and Marini 2014). Following the multicentric form, the mediastinal form is the second most common, occurring mostly at a young age of less than 1–2 years. However, the prediction of the responses and prognosis is usually challenging owing to the lack of cases with precise classification and immunological characteristics (Hammer et al. 2007; Fox and Marini 2014; Matsumoto et al. 2017). In human medicine, novel interventions, such as immunotherapy, have already been developed to overcome malignant tumours (Qin et al. 2019). However, there have been few attempts to apply these interventions for veterinary use. For these reasons, the treatment of ferret lymphomas is limited to surgical tumour resection, chemotherapy, and radiation therapy (Ammersbach et al. 2008).

Here, we describe the clinical, cytological, and histopathological features of an HLL case in a ferret. HLL was suspected based on the presence of numerous typical Reed-Sternberg (RS)-like cells in the fine-needle aspiration biopsy. We further analysed the immune-phenotypical characteristics

of the neoplastic cells in the lymph node, liver, and spleen. These characteristics were then compared to those of human HL and of a previously reported ferret HLL case to compare the prognostic factors for the new treatment options.

Case description

A 3-year-old castrated male ferret was brought to the clinic for repetitive diarrhoea and mucous faeces. On physical examination, the body condition score and hydration state seemed normal, and the superficial lymph nodes were not enlarged. On the abdominal ultrasound, the ferret was suspected to have lymphoma as the mesenteric lymph node was markedly enlarged. At initial observation, the short and long axes of the mesenteric lymph node in the patient were 14.42 mm and 27.75 mm, respectively, of which the normal thickness in ferrets is 5.3 ± 1.39 mm and 7.6 ± 2.0 mm, respectively (Suran and Wyre 2013). The node was further enlarged to 19.15 mm and 30.84 mm at the second inspection after 2 weeks (Figure 1A,B). The other organs appeared normal in the abdominal ultrasound, including the liver, spleen, kidneys, and intestines. In the complete blood count, the WBC and lymphocyte counts were $4.1 \times 10^9/l$ (normal range: 4.9–13.8) and $0.4 \times 10^9/l$ (2–6.7), respectively, indicating mild lymphopenia (Fox and Marini 2014). However, the haematocrit, haemoglobin, and RBC counts were 48.4% (33.6–47.2), 169 g/l (120–169), and $10.67 \times 10^{12}/l$ (1–10.2), respectively, which were around the upper limits of the range (Fox and Marini 2014). A serum chemistry analysis revealed no remarkable findings.

The cytological examination of a fine-needle aspiration biopsy of the mesenteric lymph node showed an increased number of medium-to-large-sized lymphocytes. These cells showed anisocytosis and anisokaryosis. The large cells were characterised by an abundant cytoplasm, oval to round nuclei with coarse chromatin, and a single, large nucleoli in the centre, resembling the morphology of immunoblasts. Binucleated or multinucleated cells were also present. We also observed Reed-Sternberg (RS)-like cells showing symmetrically arranged nuclei with a prominent single nucleolus mimicking the typical “owl eye” appearance of RS cells (Figure 1C). Upon the cytological examination, the ferret was suspected to have stage IIA alimentary

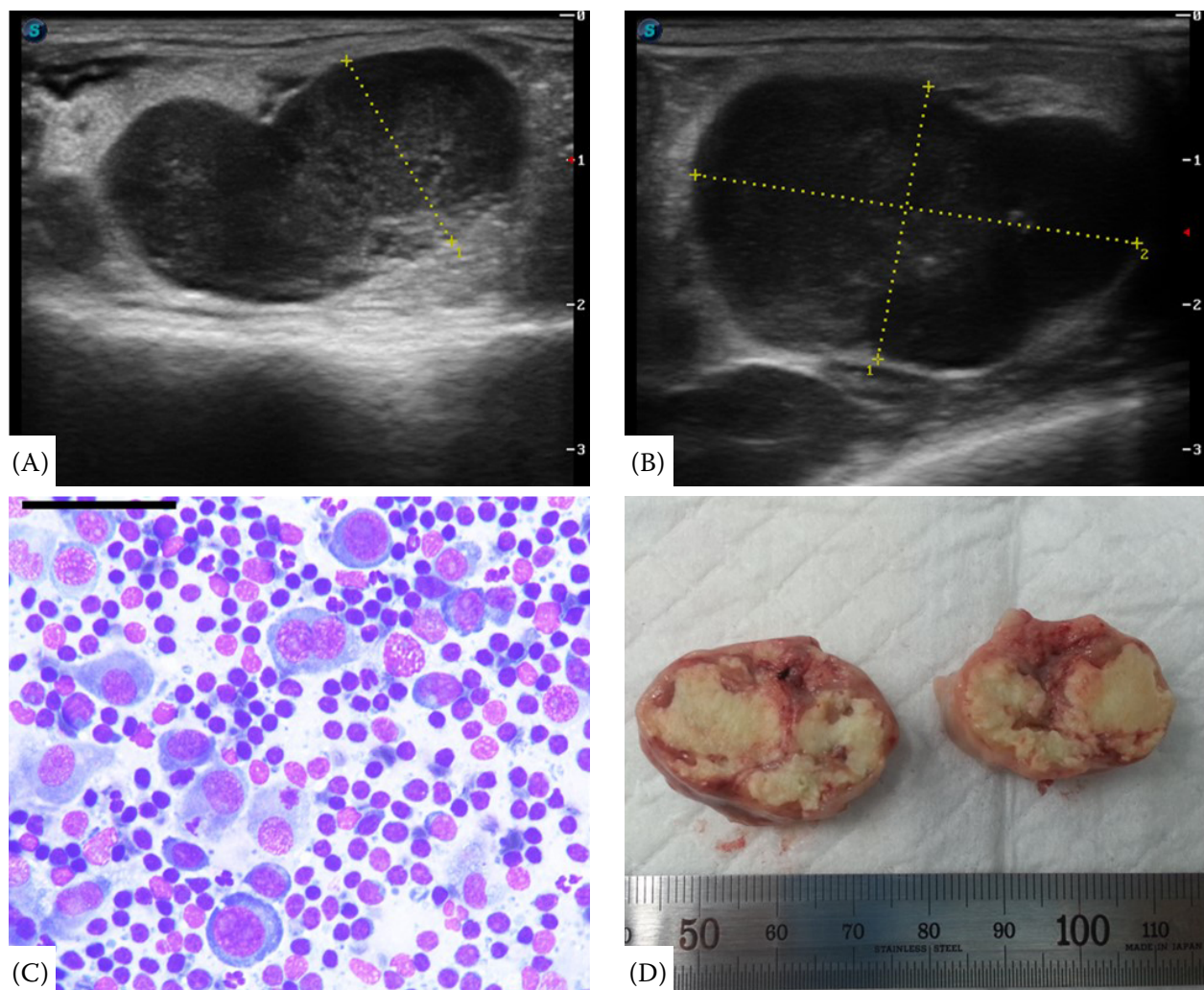


Figure 1. Ultrasonography of the mesenteric lymph node and macroscopic appearance of the affected organs after necropsy. (A,B) At initial observation, the length of the lymph node along the short axis was 14.42 mm (A), which increased to 19.15 mm (B) after 2 weeks. (C) Fine-needle aspiration cytology of the mesenteric lymph node. Diff-Quik staining. Scale bar = 50 μ m. (D) Gross appearance of the cut surface of the enlarged mesenteric lymph node

lymphoma, which is assumed to be of B-cell origin (Mayer and Burgess 2012; Sapierzynski et al. 2016).

Unfortunately, the ferret was treated with palliative fluid therapy for diarrhoea only due to the owner's limited budget. The ferret died a month later, and necropsy was performed. Upon the necropsy, the mesenteric lymph node appeared markedly enlarged with an uneven surface. A cross-section of the lymph node showed that a massive necrotic lesion had formed throughout it (Figure 1D). The spleen was enlarged with an uneven surface. The surface of the liver was relatively smooth, but the hepatic lobes were irregularly thickened.

The mesenteric lymph node, hepatic lymph node, liver, and spleen were collected, and a post-mortem histopathological examination was conducted. The

biopsy samples were fixed in 10% neutral formalin, embedded in paraffin, and cut into 4 μ m-thick sections. The sections were stained with haematoxylin and eosin for the general histological evaluation. For the immunohistochemical analysis, CD3 (Dako, Santa Clara, CA, USA; 1 : 50), CD79 α (Thermo Fisher Scientific, Waltham, MA, USA; 1 : 50), Pax5 (Thermo Fisher Scientific, Waltham, MA, USA; 1 : 50), CD20 (Thermo Fisher Scientific, Waltham, MA, USA; 1 : 50), vimentin (Dako, Santa Clara, CA, USA; 1 : 50), Iba-1 (FUJIFILM Wako Chemicals, Richmond, VA, USA; 1 : 50), BLA-36 (Dako, Santa Clara, CA, USA; ready to use), CD45 (Abcam, Cambridge, UK; 1 : 50), programmed cell death protein 1 (PD-1) (OriGene Technologies, Rockville, MD, USA; 1 : 100), and programmed death-ligand 1

(PD-L1) (Thermo Fisher Scientific, Waltham, MA, USA; 1 : 100) were used as the primary monoclonal antibodies. The antibody-labelled sections were incubated with a Vectastain Elite ABC-Peroxidase kit (Vector Laboratories, Burlingame, CA, USA). The reactions were visualised by Vector SG (Vector Laboratories, Burlingame, CA, USA) and counterstained with a nuclear fast red solution (Vector Laboratories, Burlingame, CA, USA).

The histological examination of the mesenteric lymph node revealed an infiltrative growth of the neoplastic cells and necrosis, whereas normal lymph node structures, such as the lymphatic nodules and medullary sinuses, were rarely observed. The neoplastic cells showed an infiltrative growth toward the fatty tissues in the mesentery (Figure 2A). As shown in Figure 2, the neoplastic

cells were markedly pleomorphic and larger than the small lymphocytes, showing one large or multiple prominent nucleoli. Typical cells resembling RS cells and variants, including mononucleated RS cells (Hodgkin cells), multilobed lymphocyte-predominant cells (LP cells or popcorn cells), and multinucleate cells (pleomorphic cells), were also observed (Figure 2B).

The hepatic lymph node showed a neoplastic cell infiltration in the cortex and necrosis of the medulla with the sinus ectasia. Due to the infiltration of the new cells, the nodular structure of the hepatic lymph nodes was lost, and a central necrosis was observed. The liver showed a diffuse to multifocal infiltration of tumour cells throughout the whole tissue and particularly around the portal triads. The neoplastic cells were observed within the sinusoids, intravascularly and adjacent to the vessels, resembling a diffuse intrasinusoidal to nodular growth pattern. The neoplastic cells also infiltrated the spleen, in which normal structures, including red and white pulp, were observed heterogeneously. In addition to the RS-like cells seen in the mesenteric lymph node, numerous multinucleated giant cells and multilobed lymphocytes were observed (Figure 2A).

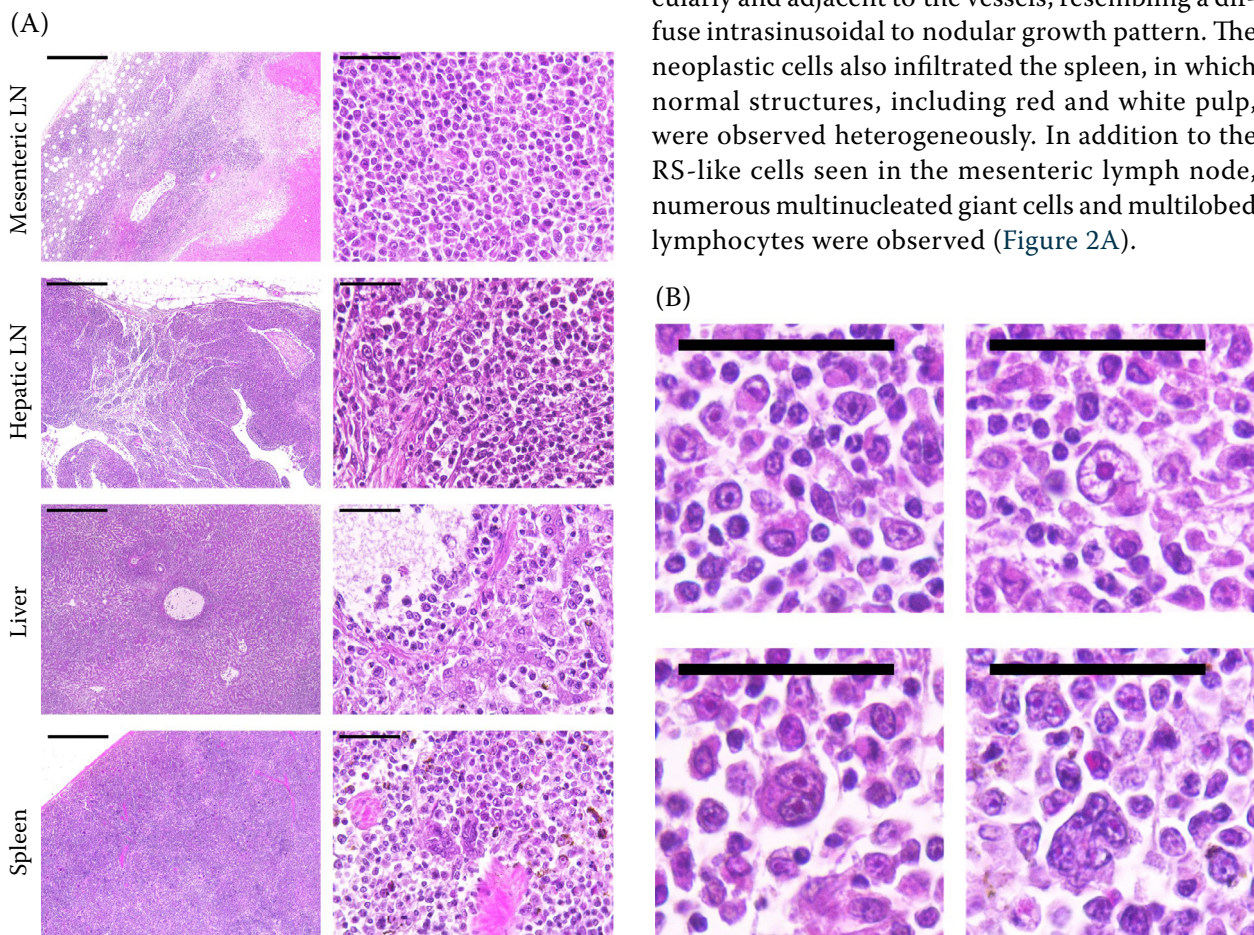


Figure 2. Histopathologic images of the submitted organs showing abnormal appearance at necropsy. (A) Microscopic images of the mesenteric lymph node, hepatic lymph node, liver, and spleen showing the diffuse infiltration of atypical lymphocytes. Scale bar = 500 μ m (left column) and 100 μ m (right column). (B) Representative images of the pleomorphic lymphocytes with one large or multiple prominent nucleoli (upper left), a mononucleated Reed-Sternberg (RS) cell (upper right), classical RS-like cell (lower left), and multilobed lymphocyte (LP cell or popcorn cell, lower right). Haematoxylin and eosin staining. Scale bar = 50 μ m

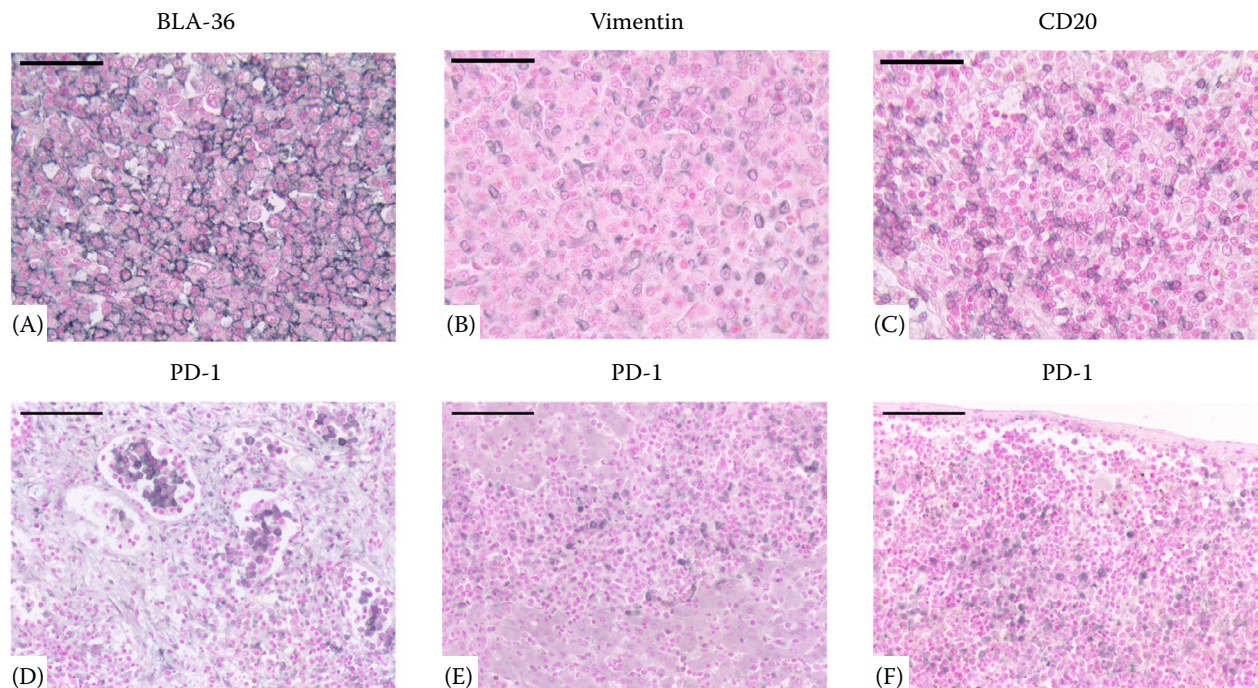


Figure 3. Immunohistochemical characterisation of the tumour cells. The neoplastic cells show positive immunoreactivity for BLA-36 (A) and vimentin (B) and partial positivity for CD20 (C). The PD-1 expression pattern is shown in the mesenteric lymph node (D), liver (E), and spleen (F). Nuclear Fast Red counterstaining. Scale bar = 50 μ m (A–C) and 100 μ m (D–F)

Immunohistochemically, most neoplastic cells were positive for vimentin and BLA-36 (Figure 3A,B). BLA-36 was also positive in the RS-like cells. Despite showing a strong positivity of BLA-36, the neoplastic cells were negative for Pax5. The neoplastic cells were also partly positive for CD20; however, the large cells with a single large nucleolus were negative for CD20 (Figure 3C). The neoplastic cells were negative for CD79 α and CD3, which were positive in the small lymphocytes between the neoplastic cells. CD45 was also negative, except in the small lymphocytes. Iba-1, which is involved in cytoskeletal rearrangement, was only positive in the histiocytes, as it is known as a pan-macrophage marker (Pierezan et al. 2014). The RS-like cells were only positive for BLA-36. The multinucleate giant cells seen in the spleen were negative for all markers except for BLA-36, which occasionally showed a positive reaction.

In the mesenteric lymph node, a PD-1 expression was found mainly in the intratumoural region beneath the necrotic lesion and not in the peritumoural region. In addition to the tumour cells, the stromal cells surrounding the lymphocytes were positive for the PD-1 expression (Figure 3D). Unlike in the mesenteric lymph node, the PD-1-expressing

tumour cells were usually found in the outer cortex of the hepatic lymph node peripheral to the necrotic region. In contrast, a positive reaction of the PD-1 antibody was found in the lymphocytes in the hepatic sinusoids, where a massive infiltration was observed (Figure 3E), and in the splenic parenchyma around the subcapsular area (Figure 3F). Moreover, we found a strong PD-1 expression in the plasma cells, classical RS-like cells, and immunoblast-like cells (large lymphocytes with abundant cytoplasm), but not in the popcorn cells. Based on these findings, it was concluded that the ferret died from multi-organ failure due to alimentary stage IVA HLL of mixed cellularity type (Pileri et al. 2002; Withrow et al. 2013; Swerdlow et al. 2016).

DISCUSSION AND CONCLUSIONS

Here, we report the cytological, histopathological, and immunohistochemical features of HLL in a domestic ferret. In addition, we first report PD-1 in an exotic animal species. Similar to human HL, the presence of RS cells could be a definitive criterion for the cytological diagnosis of HLL (Wakely 2000; Dong et al. 2001). As seen in a pre-

viously reported case of ferret HLL (Matsumoto et al. 2017), the neoplastic cells showed a positive expression of vimentin, a mesenchymal cell marker, with no expression of CD79 α , a B-cell marker (Hammer et al. 2007). These features also follow human HL characteristics, as CD79 α is rarely positive and vimentin is expressed in CHL. This can be used to differentiate between CHL and NHL, such as T-cell-rich B-cell lymphoma (TCRBCL) (Miglio et al. 2018). The expression of BLA-36, which is known to be expressed on HL and early B lymphocyte progenitor cells, was more strongly positive in the present case than in the previous case (Maeda et al. 1993). However, Pax5, a B-cell transcription factor associated with B-cell differentiation, was negative (Matsumoto et al. 2017). The CD20 expression, which is usually lost in CHL, but positive in NLPHL and TCRBCL, was negative in the large neoplastic cells (Miglio et al. 2018).

CD45, also called leukocyte common antigen, can be helpful for distinguishing between RS cells in CHL and RS-like cells, which can be found in some types of NHL, including NLPHL and TCRBCL (Miglio et al. 2018). The RS-like cells in NLPHL and TCRBCL are not true RS cells; instead, they are reactive immunoblasts with similar morphologic features. RS cells typically lack the CD45 expression, whereas RS-like cells are positive for CD45 (Pileri et al. 2002; Miglio et al. 2014). In this study, as it is difficult to confirm the expression of CD30 and CD15, which are commonly used markers for the differentiation of HL and NHL in humans, we used the CD45 expression to differentiate such features. We found that the CD45 expression was only limited to small lymphocytes, similar to that in human CHL.

Apart from what is known about human HL, the ferret HLL, in our case, displayed highly aggressive growth with the involvement of the spleen and liver. The mesenteric lymph node also showed rapid enlargement, as the long axis of the lymph node increased from 14.42 mm to 19.15 mm within 2 weeks. Moreover, the ferret died 1 month after the initial diagnosis performed by the cytological examination. Ammersbach et al. (2008) reported two cases of ferret HLL that were similar to our case showing BLA36 positivity in the RS-like cells that appeared as mono-, bi-, or multinucleated cells (Ammersbach et al. 2008). These cases were also multicentric lymphomas, and extensive necrotic lesions were formed within the lymph nodes. These HLLs displayed

a poor prognosis, and the ferrets were euthanised shortly after owing to their poor condition. The ferrets also had disseminated lesions throughout several organs (Ammersbach et al. 2008).

Ferret HL is also distinguished from that of humans by a negative Pax5 expression. Pax5 is known to be weakly expressed in RS cells and more strongly positive in NLPHL and TCRBCL. However, some studies have shown that rare cases of Pax5-negative CHL tend to be more aggressive and have a poor prognosis (Vali Betts et al. 2017).

The immunohistochemical analysis of PD-1, which is a key factor for immune system evasion, revealed that tumour cells expressing PD-1 were present in specific areas of the lesions. The outer cortex of the lymph node and spleen are common sites of tumour cells found in areas of metastasis via lymphatic vessels (Rosa et al. 2012; Karaman and Detmar 2014). The intrasinusoidal and nodular patterns of tumour cells in the liver indicate that the lymphoma was aggressive (Jaffe 1987; Loddenkemper et al. 2007). Additionally, the mesenteric lymph node microenvironment, which is a primary site of malignant neoplasm, was positive for PD-1. These findings suggest that the PD-1 expression pattern along the invasive and metastatic lesions can also be a prognostic factor of HLL in domestic ferrets and that an immune checkpoint blockade therapy could be a possible option for exotic animals such as ferrets (Gravelle et al. 2017; Moy and Younes 2018; Cioroianu et al. 2019).

Despite the features described in our case and the similarities with a previously reported case, it is difficult to concretely determine any characteristics of HLL in ferrets owing to the limited number of cases. Moreover, other immune checkpoint proteins could not be analysed properly because of the limited cross-species reactivity of various antibodies, including PD-L1, the ligand of PD-1. Although careful interpretation is needed, our findings indicate that HLL in non-humans can be morphologically and immunophenotypically similar to human HL, but the prognosis and clinical outcome may differ (Ammersbach et al. 2008).

Emerging technologies utilise circulating tumour cells and circulating tumour DNA to achieve the early detection of tumours with minimal invasiveness. Among these, flow cytometry can enhance the diagnostic value of a cytologic diagnosis without invasive diagnostics (Demurtas et al. 2010; Poggi et al. 2015). However, these methods are not

well established in veterinary medicine despite the growing need and effort to apply them (Miglio et al. 2014). We expect that these results will not only provide clues for novel diagnostic and prognostic biomarkers, but also provide a foundation for minimally invasive diagnostics.

In conclusion, our case demonstrates that lymphoma in ferrets is similar to human HL in the cytological, histopathological, and BLA-36⁺/CD20^{weak+} immunohistochemical aspects. Additionally, based on the comparison of the prognostic difference between HLL and the PD-1 expression, we suggest that PD-1 can be a prognostic factor for malignant tumours.

Additional case reports and research studies will help to elucidate HLL in ferrets as well as in other animals, therefore, leading to a more accurate diagnosis and treatment in animals.

Conflict of interest

The authors declare no conflict of interest.

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