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Lymphoma-associated hemophagocytic syndrome in six dogs

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ABSTRACT. Hemophagocytic syndrome (HPS) is a clinicopathological entity characterized by histiocytic proliferation, with marked hemophagocytosis in the reticuloendothelial organs. HPS caused by lymphoma is termed lymphoma-associated hemophagocytic syndrome (LAHS), and there are few reports on canine and feline LAHS. The objective of this study was to examine the clinical, diagnostic, and clinicopathologic features of LAHS in six dogs. The diagnostic criteria of LAHS consisted of lymphoma, bicytopenia or pancytopenia in the blood, and increased hemophagocytosis in the reticuloendothelial organs. In one dog, an ocular form of lymphoma was recognized. A splenic form was recognized in two dogs, and a hepatosplenic form was recognized in three dogs. Immunophenotyping revealed T-cell origin in five dogs and B-cell origin in one dog by polymerase chain reaction for antigen receptor rearrangement analysis. Nonspecific esterase stain was performed to differentiate between neoplastic lymphocytes and hemophagocytes. All five dogs with T-cell lymphoma were diagnosed with large granular lymphocyte (LGL) lymphoma. In three cases, palliative therapy with glucocorticoids was conducted, while the other three cases received chemotherapy as well. The survival times for the three dogs with glucocorticoids only were 6, 6, and 10 days and were 30, 54, and 68 days for the three treated with anticancer therapy. The median survival time for the dogs was 20 days. This report indicates that canine LAHS is likely to be caused by LGL lymphoma, and it has an aggressive behavior and poor general prognosis, as seen in humans.

KEY WORDS: dog, hemophagocytic syndrome, hepatosplenic T-cell lymphoma, large granular lymphocyte, lymphoma-associated hemophagocytic syndrome

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Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is a hyperinflammatory disorder resulting from immune dysfunction, reflecting either primary immune deficiency or acquired failure of normal immune homeostasis. Activated T-cells and macrophages secrete high levels of inflammatory cytokines that are associated with multiple cytopenias in the blood [19, 21]. In humans, HPS is divided into primary and secondary HPS. Primary HPS is associated with genetic mutations and usually appears in childhood, while secondary HPS is associated with a variety of underlying conditions and is more common in adults. Secondary HPS is caused by various diseases, such as viral infections (virus-associated hemophagocytic syndrome: VAHS); bacterial infections (bacteria-associated hemophagocytic syndrome: BAHS), including tuberculosis; fungal infections; autoimmune disorders (autoimmune-associated hemophagocytic syndrome: AAHS); and malignant lymphoma (lymphoma-associated hemophagocytic syndrome: LAHS). A diagnostic of HPS is established according to the International Histiocyte Society HLH-2004 diagnostic criteria when five of the eight following clinical criteria are present: (1) fever, (2) splenomegaly, (3) cytopenias affecting two or three lineages, (4) hypertriglyceridemia, (5) hemophagocytosis in the bone marrow, spleen, or lymph nodes, (6) hyperferritinemia, (7) low or absent natural killer (NK) cell activity, and (8) soluble CD25 ≥2,400 U/m*l* [10]. In dogs, there are few reports on HPS, but one previous report showed that canine HPS is caused by infections, autoimmune disorders, and malignant disorders [21]. The criteria for a diagnosis of canine HPS in previous reports consisted of bicytopenia or pancytopenia in the blood and >2% hemophagocytic macrophages in bone marrow aspirates [19–21].

According to the latest human studies, mainly from Asian countries, the incidence of LAHS is more common than those of other types of HPS [15]. Most cases of LAHS are associated with T-cell or NK/T-cell lymphoma. LAHS secondary to B-cell lymphoma is quite rare and has a worse prognosis than B-cell lymphoma alone [8]. A previous report revealed that the overall survival rate of LAHS was low, and that the patients died within several months unless they received chemotherapy [15]. Canine and feline LAHS has not been frequently described in veterinary literature [3, 6]. Therefore, the objective of this study was to examine the clinical, diagnostic, and clinicopathologic features of LAHS in six dogs.

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Table 1. Data on bleed, signalment, with or without splenomegaly and affected organs of six dogs with LAHS

No.	Bleed	Signalement			Splenomegaly	Affected organs			
		Sex	Age (year)	BT (°C)		Liver	Spleen	Bone marrow (hemophagocytes, %)	Other organs
1	Mix	FS	4	39.7	-	ND	ND	+ (2.6)	Eye
2	Mix	M	13	40.0	+	ND	+	+ (5.4)	
3	American coker spaniel	S	5	38.4	+	ND	+	ND	
4	Shih Tzu	M	6	39.4	+	+	+	+ (6.4)	
5	Bernese mountain dog	M	7	38.7	+	+	+	ND	
6	Japanese spitz	M	12	39.3	+	+	+	ND	Abdominal lymph nodes

FS, female spayed; M, male; F, female; BT, body temperature; ND, not done.

MATERIALS AND METHODS

This retrospective study was conducted on dogs that were patients of the Sanyo Animal Medical Center in Japan. The cases were identified retrospectively by searching the medical records for the period of 2007–2016. Data on signalment, clinical signs, results of hematologic examination and imaging techniques, main pathology, cytological examination, PCR for antigen receptor rearrangements (PARR), treatment, survival time, and cause of death were recorded in each case. Anemia, neutropenia, and thrombocytopenia were defined as HCT <36%, neutrophil count <3,000/μl, and platelet count <200,000/μl in the absence of platelet aggregates, respectively [22]. Cytological samples were obtained by bone marrow aspiration or ultrasound-guided fine-needle aspiration (FNA) of the liver and/or spleen. Aspirated material was spread on glass slides, air-dried, and stained with Wright-Giemsa and nonspecific esterase (NSE). The NSE stain is a rust-red, diffuse reaction for α-naphthyl butyrate esterase (ANBE), which is inhibited by sodium fluoride (NaF), used to distinguish monocytes from other leukocytes in the smear [2, 22]. Criteria for a diagnosis of LAHS consisted of the presence of lymphoma, bicytopenia or pancytopenia in the blood, and increased hemophagocytosis in the organs of the reticuloendothelial system (the bone marrow, spleen, or liver), in accordance with the described method [14, 16]. The choice of therapy was clinically dependent. Because the majority of cases had no measurable lesion, it is difficult to evaluate the response to treatments according to established response criteria.

RESULTS

During the period from 2007 to 2016, six dogs were recognized as having LAHS. The six dogs were all referral cases from other animal hospitals, and some had been treated with corticosteroids (dogs 3, 4) or antibiotics (dogs 2, 5). Breeds represented were American Cocker Spaniel (n=1), Shih Tzu (n=1), Bernese Mountain Dog (n=1), Japanese Spitz (n=1), and mixed breed dog (n=2). The median age of the patients was 6.5 years (range, 4–13 years), and median body weight was 10.0 kg (range, 5.7–40.9 kg). Four dogs were intact males, one dog was an intact female, and the remaining dog was a spayed female. Four of the six dogs presented with fever, and five had splenomegaly. Bicytopenia was observed in four dogs (three dogs had nonregenerative anemia and thrombocytopenia, while one dog had neutropenia and thrombocytopenia), and pancytopenia was observed in the other two dogs at the time of diagnosis. Three of the six dogs had FNA of the liver performed by ultrasound-guided, which was interpreted as lymphoma with hemophagocytosis in all dogs. Five dogs with splenomegaly had splenic aspirates, and all were interpreted as lymphoma with hemophagocytosis. Bone marrow aspiration was performed in three of the six dogs. All three dogs had >2% hemophagocytes in the bone marrow. The breed, sex, age, body temperature at first visit, presence of splenomegaly, affected organ(s), and rate of hemophagocytes in all nucleated bone marrow cells (ANC) in each case are listed in Table 1.

For cytological examination of the dogs, except for Dog 3, the neoplastic lymphocytes were intermediate to large in size and had round, oval, indented, or irregularly shaped nuclei from 1.5 to 3.0 red blood cells (RBCs) in diameter. Nuclei had finely stippled chromatin and variably prominent nucleoli. There was abundant pale cytoplasm containing fine vacuoles and variable numbers of azurophilic to basophilic cytoplasmic granules. In Dog 3, the neoplastic lymphocytes were large in size with nuclei 3.0 RBCs in diameter and had abundant blue cytoplasm without cytoplasmic granules. Nuclei were round or reniform. The chromatin was densely stained and uniformly distributed, with nucleoli not apparent. Macrophages containing erythrocytes, neutrophils, and platelets were noted in all six dogs. The cells were large and had atypical features, including fine nuclear chromatin, multiple nucleoli, and occasional azurophilic cytoplasmic granules. In Dogs 3 and 6, hemophagia was noted in the neoplastic lymphocytes and the attendant hyperplastic macrophage population. On review of available NSE-stained smears, hemophagocytes were stained positive for NSE, and the NSE activities were inhibited by the addition of NaF in all five dogs (Dogs 1–5). The neoplastic lymphocytes were stained negative for NSE in Dogs 1, 3, and 4. In Dog 2, the neoplastic lymphocytes were positive for NSE staining that was inhibited by NaF addition. In Dog 5, the neoplastic lymphocytes were positive for NSE that was not inhibited by the NaF. The PARR analysis of the FNA and/or bone marrow samples demonstrated that Dog 3 was determined as B-cell origin and the other patients were T-cell origin. All five dogs with T-cell origin were regarded as LGL lymphoma. According to the anatomical classification, in one dog, an ocular form of lymphoma was recognized. A splenic form was recognized in two dogs, and a hepatosplenic form was recognized in three dogs. Cytological features and result of PARR analysis are listed in Fig. 1 and Table 2.

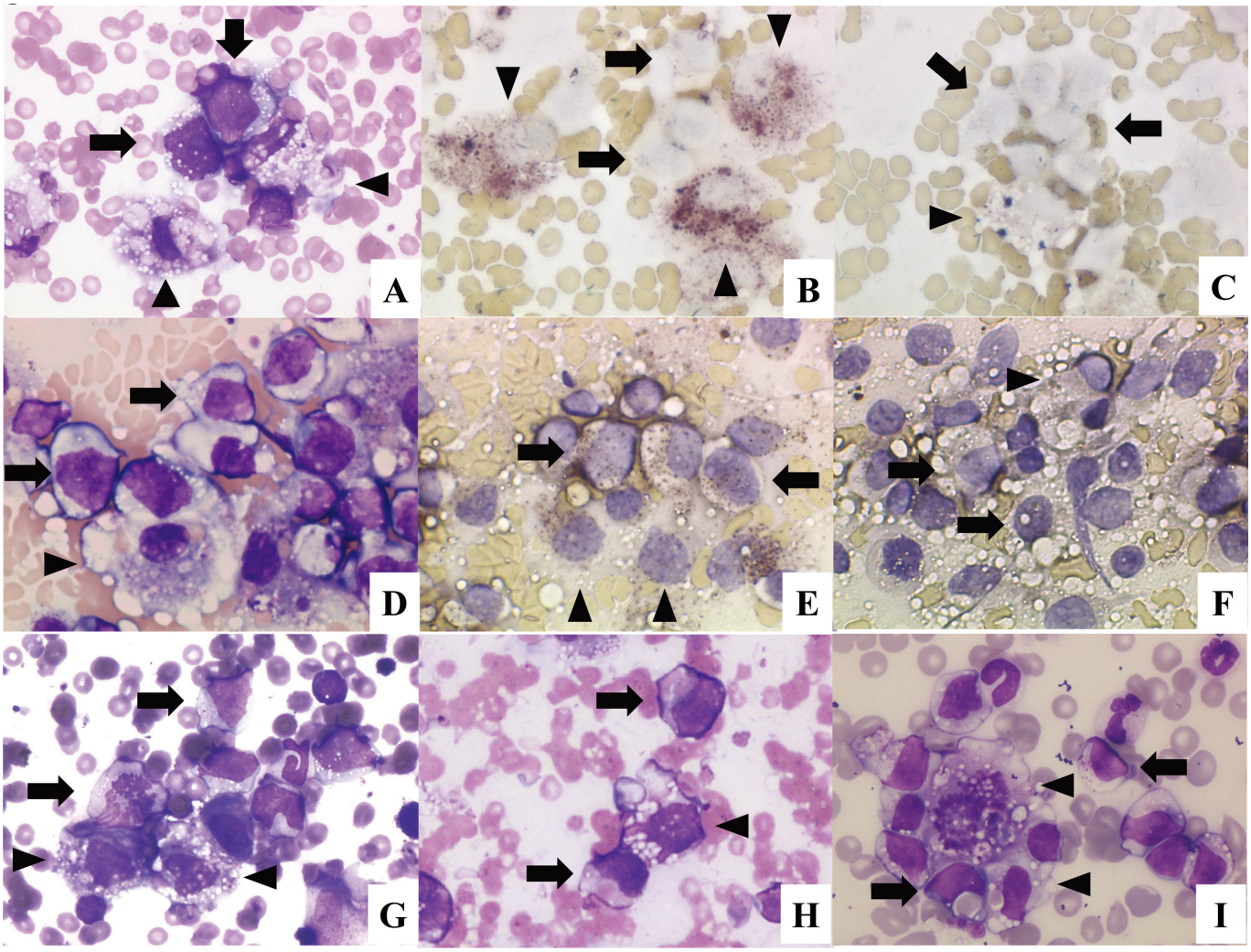

Fig. 1. Cytological features of LAHS. The neoplastic lymphocytes are indicated by arrows and the hemophagocytes are indicated by arrowheads. A–C: Bone marrow aspiration in Dog 4. (A) Wright-Giemsa staining at 400×. Neoplastic lymphocytes have immature morphology, characterized by large size and some nucleoli. These cells possess pale cytoplasm containing fine vacuoles and variable numbers of azurophilic to basophilic cytoplasmic granules. (B) NSE staining at 400×. Neoplastic lymphocytes stained negative for NSE. Hemophagocytes stained positive. (C) The addition of NaF at 400×. NSE activities of hemophagocytes were inhibited by the addition of NaF. D–F: Bone marrow aspiration in Dog 2. (D) Wright-Giemsa staining at 400×. Neoplastic lymphocytes have immature morphology, characterized by medium size, and some nucleoli. These cells possess abundant pale cytoplasm containing fine vacuoles and cytoplasmic granules. (E) NSE staining at 400×. Both neoplastic lymphocytes and hemophagocytes stained positive for NSE. (F) The addition of NaF at 400×. NSE activities of both cells were inhibited by the addition of NaF. G: Bone marrow aspiration in Dog 1 (Wright-Giemsa staining at 400×). Neoplastic lymphocytes with mitotic activity are seen. H: Cytology of the spleen in Dog 3 (Wright-Giemsa staining at 400×). Hemophagia was noted in both neoplastic lymphocytes and macrophages. I: Cytology of the liver in Dog 6 (Wright-Giemsa staining at 400×). Hemophagia was noted in both neoplastic lymphocytes and macrophages, as seen in Dog 3.

Dog 1 was treated with lomustine (CCNU), cyclosporine A (CyA), and prednisolone (PSL). Dog 2 was treated with CCNU and PSL, and Dog 6 was treated with UW-25 (the University of Wisconsin-Madison protocol) [7]. The other three cases were treated with only PSL. The median survival time (MST) for the six dogs with the various treatments was 20 days (range, 6–68 days). The survival times for the three dogs that received anticancer therapy were 30, 54, and 68 days. The survival times for the three dogs with PSL only were 6, 6, and 10 days. Specific data on the mode of blood cell count at the time of diagnosis, therapy, survival time, and cause of death are presented in Table 3.

DISCUSSION

Among the wide range of clinical diseases that cause HPS in humans, lymphoma is one of the most frequent [12, 14, 15, 17]. However, there have been few reports on LAHS in dogs, and in one study including 24 dogs with HPS, only two cases without detailed clinical information were caused by lymphoma [21]. The criteria for a diagnosis of canine HPS in previous reports

Table 2. The NSE staining features of the neoplastic lymphocytes and hemophagocytes, and results of PARR analysis of six dogs with LAHS

No.	Neoplastic lymphocytes				Hemophagocytes	
	NSE	NaF inhibitation	Cytoplasmic granules	PARR	NSE	NaF inhibitation
1	-	-	+	T	+	+
2	+	+	+	T	+	+
3	-	-	-	B	+	+
4	-	-	+	T	+	+
5	+	-	+	T	+	+
6	ND	ND	+	T	ND	ND

ND, not done.

Table 3. Particular data on mode of cell blood count at the time of diagnosis, therapy, effect of therapy, survival time, and cause of death in six dogs with LAHS

No.	HCT (%)	Reticulocytes/μl	Platelets/μl	Neutrophils/μl	Therapy	Survival time (day)	Cause of death
1	37.1	18,570	71,000	1,930	CCNU, CyA	54	Anemia, thrombocytopenia
2	21.0	53,250	8,000	8,325	CCNU	30	
3	10.0	48,900	25,000	2,391	PSL	10	
4	11.1	50,120	9,000	100	PSL	6	
5	15.6	33,000	70,000	14,520	PSL	6	
6	20.7	84,840	59,000	10,060	UW25	68	
Reference interval	37–55	<70,000	200,000–500,000	3,000–11,500			

CCNU, lomustine; CyA, cyclosporine A; PSL, prednisolone.

consisted of bicytopenia or pancytopenia in the blood and >2% hemophagocytic macrophages in bone marrow aspirates [18–21]. However, these diagnostic guidelines have not yet been widely accepted. In humans, hemophagocytosis in the organs of the reticuloendothelial system is one of the criteria for a diagnosis of HPS, and bone marrow aspiration is not necessary for the diagnosis. For the diagnosis of canine LAHS, we defined the following criteria by altering the previous human reports [14, 16]: (1) presence of lymphoma, (2) bicytopenia or pancytopenia in the blood, and (3) increased hemophagocytosis in the reticuloendothelial organs (the bone marrow, spleen, or liver). In this study, three cases underwent bone marrow aspiration and had >2% hemophagocytes in ANC. The three cases without bone marrow aspiration had increased hemophagocytes in the reticuloendothelial organs (spleen and/or liver). On the other hand, these findings must be interpreted with caution, because the absolute value of hemophagocytes in the reticuloendothelial systems was not assessed. This is an important issue for future research.

In these cases, four of the six dogs presented with fever, which is one of the diagnostic criteria of HPS in humans [10]. The normal body temperature of the other two dogs may have been due to previous treatment with corticosteroids or antibiotics at the referring hospitals.

In humans, most cases of LAHS have been known to be associated with T-cell or NK/T-cell lymphoma. A previous report of 29 patients with T-cell or NK/T-cell LAHS revealed that in the NK/T-cell lymphoma group, 11 patients were diagnosed with extranodal NK/T-cell lymphoma, nasal type (NKTCL), and four patients were defined as having aggressive NK-cell leukemia (ANKCL). In the T-cell lymphoma group, six patients were diagnosed with peripheral T-cell lymphoma (PTCL), not otherwise specified (PTCL-NOS); five with systemic anaplastic large cell lymphoma (ALCL); two with subcutaneous panniculitis like T-cell lymphoma (SPTCL); and one with hepatosplenic T-cell lymphoma (HSTL) [9, 12, 14, 15]. In the previous reports of canine HSTL, erythrophagocytosis by neoplastic lymphocytes and a concurrent hyperplastic population of macrophages were a consistent feature in HSTL [4, 6, 11]. In practice, these macrophages should be termed as not “erythrophagocytes” but rather “hemophagocytes,” because these macrophages include erythrocytes, neutrophils, and platelets. HSTL with concurrent hemophagocytosis and bicytopenia or pancytopenia (mostly bicytopenia involving anemia and thrombocytopenia) indicates concurrent HPS and is associated with a rapid clinical deterioration in humans [5]. In the study involving nine cases of dogs with HSTL, almost all cases had recognized hemophagocytosis in the liver or spleen, and seven of the cases had bicytopenia, characterized by anemia and thrombocytopenia. The MST for the dogs was 4 days. It has been described that HSTL in dogs most likely originates from CD11d+ splenic red pulp γδ T-cells [11]. In the present study, half of the cases were interpreted as HSTL, and MST for these dogs was 6 days. In three of the cases, FNA of the liver and spleen was not performed. Thus, more of the cases may have involved HSTL. These results revealed that canine HSTL is one cause of LAHS and was associated with a rapid clinical course and poor prognosis, as seen in humans. Although HSTL is difficult to diagnose due to nonspecific clinicopathological features, its diagnosis can be made earlier by performing cytological examination of the liver and spleen if bicytopenia or pancytopenia is present in the blood. In addition to HSTL, B-cell lymphoma and ocular form of lymphoma were identified in this study. To our knowledge, these were

the first cases of canine LAHS with causes other than HSTL.

In dogs, hemophagia has been reported to occur in individual cases of mast cell and plasma cell tumors, megakaryocytic leukemia, and hemophagocytic histiocytic sarcoma [1]. Therefore, cytologic differentiation of benign and malignant forms of HPS can be problematic. The previous study of the cytologic evaluation of benign and malignant hemophagocytic disorders in canine bone marrow has reported that the cytomorphologic evaluation of the bone marrow alone might not be adequate to consistently differentiate these cells [19]. Another study has described that the cellular distribution in scatter plots and the total number of macrophages in the bone marrow might be useful in differentiating malignant histiocytosis from benign HPS in dogs [20]. In the present study, we evaluated the capability of NSE stain to differentiate between neoplastic lymphocytes and hemophagocytes. The NSE staining of monocytes, granulocytes, and a subset of lymphocytes exhibited unique patterns of activity. A red to pinkish brown, diffusely granular pattern was seen in monocytes, while macrophages stained more intensely, and a single focal or punctate reaction product was seen in T-lymphocytes. The NSE activity in monocytes was inhibited by the addition of NaF to the incubation medium, whereas T-lymphocytes were resistant. Differentiated histiocytes or macrophages had weakened or abolished reactivity in the presence of sufficient NaF [22]. In all five dogs with NSE stain, the hemophagocytes stained strongly for NSE activity that was inhibited by the addition of NaF. This result indicated that the hemophagocytes were of monocyte or macrophage origin. In four of the dogs, these neoplastic lymphocytes stained differently for NSE than the hemophagocytes, thus we were able to differentiate the cells. In Dog 2, the neoplastic lymphocytes had different cytomorphologic features from the hemophagocytes and were revealed as T-cell origin by the PARR analysis. Accordingly, Dog 2 was diagnosed with LAHS. In Dog 5, the neoplastic cells were stained diffusely for NSE activity that was resistant to the addition of NaF. As a result, the neoplastic cells were determined to be either T-lymphocytes or histiocytes. The cells were then comprehensively interpreted as lymphocytes by the cytomorphologic features and the result of PARR analysis. These findings may be somewhat limited for differentiating lymphoma from other diseases, such as histiocytic sarcoma, because the PARR may cause a false positive and the NSE stain obtained slight variation between individuals. Further studies are needed in order to improve the diagnostic accuracy of using flow cytometric evaluation and/or immunohistochemical staining of the FNA samples.

Treatment for LAHS is still under investigation. In humans, the patients were given various kind of therapy, such as chemotherapy, cyclosporine, and corticosteroid [9, 14]. But NK/T-LAHS is a disease with poor prognosis and high mortality. The MST for the six dogs with LAHS was very short, as seen in previous reports in humans and dogs. The survival times for the three dogs with anticancer therapy were 30, 54, and 68 days. Dog 1 received CCNU and concurrent immunosuppressive drugs, CyA and PSL. Dog 2 was treated with CCNU and PSL. Dog 6 was treated with UW-25. The survival times for the three dogs (Dogs 4, 5, and 6) treated with PSL only were 6, 6, and 10 days, respectively. It is unclear from this small number of dogs whether chemotherapy and immunosuppressive drugs are effective for LAHS; however, it has been described that once the diagnosis of LAHS is confirmed, treatment for lymphoma and HPS are both of paramount importance in humans [9].

There has been one report of erythrophagocytic low-grade HSTL in a cat. In this case, cytopenia in the blood was not seen, and the cat lived longer than 2.5 years [3]. This report was a feline case and involved low-grade lymphoma; however, it may indicate the possibility of improving the prognosis if hemophagocytosis is diagnosed early, so that treatment can begin before cytopenia occurs.

Several limitations should be considered when interpreting our results. Because of the nature of our retrospective study, cytological examination of the bone marrow, liver, and spleen was not performed in all cases. Histological examination to classify the disease according to the World Health Organization (WHO) system was not performed in any of the cases [13]. The treatments for LAHS were not consecutive in each case, and the study involves only a small number of dogs with LAHS. To resolve these problems, prospective studies are needed to investigate further the features of LAHS in dogs.

In conclusion, canine LAHS had some clinical features in this study. Almost of dogs had fever, splenomegaly, and T-cell lymphoma with LGL. Half of the cases were interpreted as HSTL. Overall, the dogs with LAHS had a poor survival despite treatments. These results are similar to LAHS in humans [8–10, 14, 15]. In addition, LAHS should be included early in the differential diagnosis of bicytopenia or pancytopenia in the blood, along with either neoplastic lymphocytes or hemophagocytes. After diagnosis, treatment with both chemotherapy for lymphoma and immunosuppressive therapy for HPS may be needed to improve survival times. Assessment of a larger number of cases is required to further characterize the biologic behavior, improve the diagnostic accuracy, and determine the expected survival times and associated risk factors of LAHS in dogs.

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