

Case report: Haemophagocytic histiocytic sarcoma in an english setter

Mikael Kerboeuf  | Hege Brun-Hansen | Malin Oscarson | Heidi Sjetne Lund

Faculty of Veterinary Medicine, Norwegian University of Life sciences, Oslo, Norway

Correspondence

Mikael Kerboeuf, Norwegian University of Life sciences, Faculty of Veterinary Medicine, Oslo, Norway.
Email: mikael.mathias.kerboeuf@nmbu.no

Abstract

A 4-year-old English setter presented with a 1-week history of anorexia, lethargy and occasional vomiting. Blood analysis revealed moderate regenerative anaemia, mild monocytosis, thrombocytopaenia, hypoproteinaemia, hypoglobulinaemia, hypocholesterolaemia and increased C-reactive protein. On ultrasonography, the spleen had multifocal hypoechoic lesions. Fine needle aspirates from the spleen and liver showed marked extramedullary haematopoiesis, an increased number of histiocytes, haemosiderin deposits and erythrophagocytosis. A tentative diagnosis of haemophagocytic histiocytic sarcoma (HHS) was made, and the owners elected euthanasia. On autopsy, the liver and spleen were enlarged. The spleen had an uneven surface and a yellow-tan spotted appearance. Histologically, the red pulp was highly cellular and dominated by erythroid cells, as well as a population of larger polygonal cells and aggregates of histiocytes. HHS was confirmed by CD11d immunolabelling. This represents the first documented case of HHS in an English setter.

KEYWORDS

anaemia, canine, HHS, immunohistochemistry, spleen

1 | CASE PRESENTATION

A 4-year-old English setter, intact male, was referred to the Small Animal Clinic at the Norwegian University of Life Sciences in Oslo, Norway, due to a 1-week history of anorexia, progressive lethargy and occasional vomiting. The dog was fully vaccinated and had no history of travel, previous disease or medication. Upon presentation, the dog was lethargic with pale and tacky mucous membranes, a heart rate of 120 beats per minute and thready femoral pulses. On palpation, the abdomen was distended but not painful. Physical examination was otherwise unremarkable.

A complete blood count showed a moderate normocytic normochromic regenerative anaemia, mild monocytosis and mild thrombocytopenia, which was confirmed on blood smear examination (Table 1). Serum biochemistry showed a mild hypoproteinaemia,

mild hypoglobulinaemia, mild hypocholesterolaemia and moderately increased C-reactive protein (Table 1). Activated partial thromboplastin time and prothrombin time were not prolonged (aPTT 67s, reference 72–102 s, PT 14s, reference 11–17 s, IDEXX Coag Dx Analyzer). Urinalysis revealed a moderate bilirubinuria (100 µmol/L, IDEXX UA Strip). On abdominal ultrasound performed by a board-certified radiologist, the spleen had moderately rounded margins with mild diffuse reduced echogenicity and multifocal, ill-defined, slightly hypoechoic lesions scattered throughout the entire parenchyma. The splenic lymph nodes were slightly enlarged. Thoracic radiographs were unremarkable.

Cytology smears from the spleen and liver were evaluated by a board-certified clinical pathologist. Splenic cytology was highly cellular and dominated by erythroid precursor cells, but also low numbers of myeloid precursor cells and high numbers of megakaryocytes.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Veterinary Medicine and Science* published by John Wiley & Sons Ltd.

TABLE 1 Haematology and biochemistry values from day 1, 4 and 5 from a dog with haemophagocytic histiocytic sarcoma

	Day 1	Day 4	Day 5
RBC ($\times 10^{12}/L$)	†3.86 (5.65–8.87)	†4.11 (5.1–8.5)	†2.87 (5.1–8.5)
HCT (%)	†27.5 (37.3–61.7)	†33.0 (35.0–55.0)	†25.0 (35.0–55.0)
HGB (g/dL)	†9.3 (13.1–20.5)	†10.5 (12.0–18.0)	†7.4 (12.0–18.0)
MCV (fL)	71.2 (61.6–73.5)	†81.1 (62–76)	†85.7 (62–76)
MCHC (g/dL)	33.8 (32.0–37.9)	†31.5 (32.0–36.0)	†29.9 (32.0–36.0)
RDW (%)	18.3 (13.6–21.7)	16.0 (11–16)	15.2 (11–16)
Retic ($\times 10^9/L$)	†243.6 (10.0–110)	†409 (10.0–110)	†265 (10.0–110)
WBC ($\times 10^9/L$)	15.70 (5.05–16.76)	12.6 (6.0–18.0)	12.5 (6.0–18.0)
Neu ($\times 10^9/L$)	10.48 (2.95–11.64)	8.5 (3.6–13.0)	8.1 (3.6–13.0)
Lym ($\times 10^9/L$)	2.58 (1.05–5.1)	2.1 (0.8–5.8)	3.0 (0.8–5.8)
Mono ($\times 10^9/L$)	†2.34 (0.16–1.12)	1.5 (0–1.6)	0.9 (0–1.6)
Eos ($\times 10^9/L$)	0.29 (0.06–1.23)	0.4 (0–1.8)	0.5 (0–1.8)
Baso ($\times 10^9/L$)	0.01 (0.00–0.10)	0.0 (0–0.4)	0.0 (0–0.4)
PLT ($\times 10^9/L$)	†128 (148–484)	†120 (180–500)	†108 (180–500)
GLU (mmol/L)	5.41 (4.11–7.95)	5.1 (3.6–6.6)	4.7 (3.6–6.6)
CREA ($\mu\text{mol}/L$)	64 (44–159)	73 (65–110)	57 (65–110)
UREA (mmol/L)	2.7 (2.5–9.6)	5.0 (3.5–7.2)	†2.3 (3.5–7.2)
PHOS (mmol/L)	0.92 (0.81–2.20)	1.2 (0.9–2.0)	1.3 (0.9–2.0)
CA (mmol/L)	2.08 (1.98–3.00)	2.3 (2.2–2.9)	2.2 (2.2–2.9)
TP (g/L)	†48 (52–82)	†49 (54–75)	†41 (54–75)
ALB (g/L)	24 (23–40)	†30 (32–44)	†24 (32–44)
GLOB (g/L)	†24 (25–45)	†19 (22–31)	†17 (22–31)
ALB/GLOB	1.0	1.58 (1.0–2.0)	1.41 (1.0–2.0)
ALT (U/L)	53 (10–125)	19 (0–80)	36 (0–80)
AST (U/L)		19 (0–40)	24 (0–40)
ALKP (U/L)	27 (23–212)	18 (0–90)	14 (0–90)
CK (U/L)		198 (0–200)	†314 (0–200)
Bile acid ($\mu\text{mol}/L$)		1 (0–10)	1 (0–10)
TBIL ($\mu\text{mol}/L$)	5 (0–15)	6 (0–7)	5 (0–7)
CHOL (mmol/L)	†2.15 (2.84–8.26)	†2.7 (3.4–10.0)	†2.2 (3.4–10.0)
AMYL (U/L)	962 (500–1500)	970 (0–1050)	861 (0–1050)
LIPA (U/L)	237 (200–1800)	11 (0–150)	7 (0–150)
Na (mmol/L)	151 (144–160)	148 (140–154)	147 (140–154)
K (mmol/L)	4.2 (3.5–5.8)	4.4 (3.7–5.8)	4.5 (3.7–5.8)
Cl (mmol/L)	112 (109–122)	115 (99–115)	†118 (99–115)
CRP (mg/L)	†84.6 (0.0–10.0)	†71.5 (0–15)	†67.9 (0–15)

Note: Values from day 1 were obtained with the IDEXX ProCyte Dx Haematology Analyser and Catalyst Dx Chemistry Analyser. Values from day 4 and 5 were obtained from the reference laboratory at the Norwegian University of Life Sciences. All values are listed with the analyser's own reference values. Values outside the reference range are marked with †.

There were also moderately to markedly increased numbers of round to spindle cells with ill-defined cytoplasmic borders. Some of these cells had a histiocytic appearance, with a moderate to marked increase in nuclear/cytoplasmic ratio and a lightly blue coloured cytoplasm. Some contained haemosiderin and some were erythrophagocytic (Figure 1). Their nuclei were round to oval with finely

stippled chromatin, with zero to four nucleoli. There was moderate anisokaryosis and scattered mitoses. Similar cells were also present in the smears from the liver.

Despite initial cardiovascular stabilization and antiemetic treatment with maropitant 1 mg/kg (Cerenia; Zoetis) once daily, the dog did not improve further. Nevertheless, the owner wanted to take the

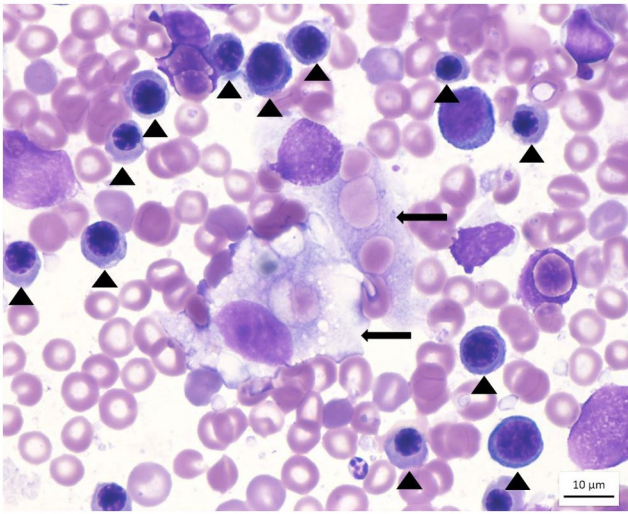


FIGURE 1 Cytology from the spleen. Mesenchymal cells showing erythrophagocytosis (arrows). Multiple erythroid precursor cells (arrowheads) can be seen in the background. Hemacolor® Rapid stain. 100x objective

dog home for the remainder of the weekend, where no improvement was noted. Physical examination on day 4 revealed that the dog had become painful on abdominal palpation and mildly dehydrated. Blood analysis results from day 4 and 5 are summarized in Table 1. There was no sign of spherocytosis or auto-agglutination on blood smears. Due to the dog's deteriorating condition and a tentative diagnosis of haemophagocytic histiocytic sarcoma (HHS), the owners elected euthanasia.

At autopsy, the dog had a moderately enlarged liver with rounded edges, reduced texture and reticular appearance. The spleen was markedly enlarged with rounded edges, an uneven surface and a yellow-tan spotted appearance. Histologically, the spleen had sparse amounts of white pulp and a highly cellular red pulp. The red pulp was dominated by small confluent aggregates of erythroid cells, with a population of larger polygonal to ovoid cells with a blast-like appearance, with basophilic cytoplasm and large circular nuclei with one to two nucleoli. There were multifocal small aggregates of well-differentiated histiocytic cells, many containing haemosiderin and some showing erythrophagocytosis. In the liver, there were aggregates of erythroid cells periportally and multifocally in the sinusoids, as well as some well-differentiated histiocytes periportally, some of which showed erythrophagocytosis. There were few neoplastic macrophages in the bone marrow and the lungs, and unidentified small round cells with hyperchromatic nuclei within some alveolar septa. The bone marrow was dominated by erythroid precursor cells, mostly rubricytes and some blasts, with scattered megakaryocytes and low numbers of myeloid and monocytic precursor cells.

Immunohistochemical labelling for CD11d was performed on formalin-fixed, paraffin-embedded tissue from the spleen, liver and lungs at an external pathology laboratory (University of California, Davis). The spleen showed large infiltrates of CD11d + histiocytes throughout the splenic parenchyma. In the liver, there were high numbers of CD11d + cells in the sinusoids (Figure 2), with some

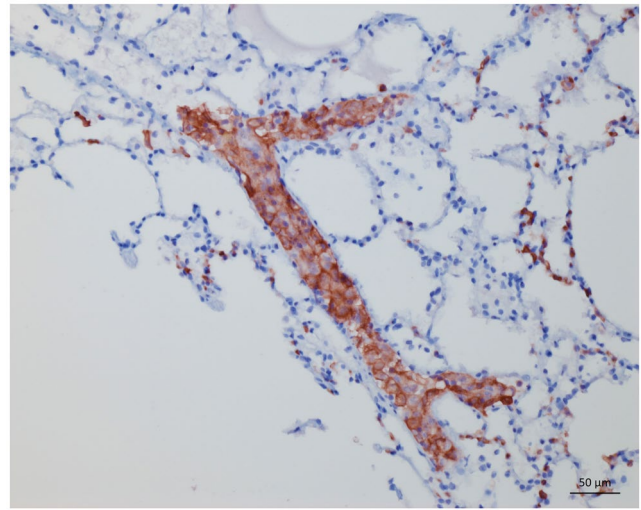


FIGURE 2 Formalin-fixed paraffin-embedded tissue, Lungs. CD11d expressing tumour embolism within a pulmonary arterial vessel and surrounding alveolar septal infiltration. Immunoperoxidase stain for CD11d; DAB chromogen and haematoxylin counterstain. 20x objective

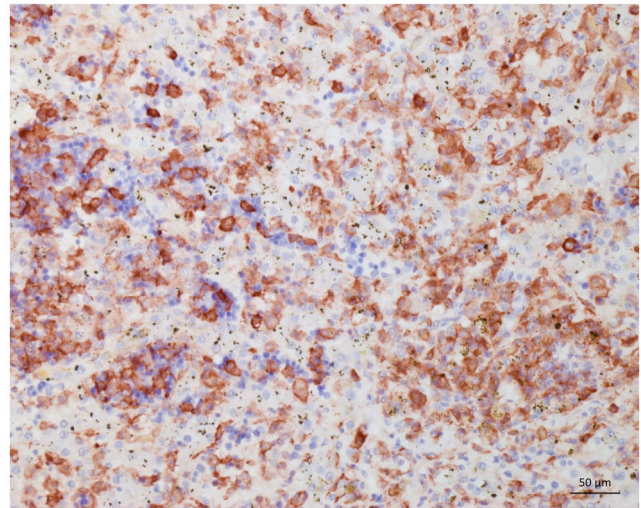


FIGURE 3 Formalin-fixed paraffin-embedded tissue, Liver. Diffuse expression of CD11d by tumour cell infiltrates in the sinusoids of the liver. Dark pigment (haemosiderin) can be seen throughout the section. Immunoperoxidase stain for CD11d; DAB chromogen and haematoxylin counterstain. 20x objective

areas showing foci of coalescing histiocytes. In the lungs, there were moderate amounts of CD11d + cells in the alveolar septa, as well as aggregates of CD11d + cells within pulmonary arterioles, sometimes forming neoplastic emboli (Figure 3).

2 | DISCUSSION

Histiocytic proliferative disorders are common in dogs. Most of these disorders involve dendritic cell proliferation (Affolter &

Moore, 2002; Moore, 2014). They may, however, also originate from splenic red pulp- or bone marrow CD11d + macrophages and result in an uncommon disorder known as HHS, resulting in a distinctive set of clinicopathological findings (Moore, 2014; Moore et al., 2006). There is only one case series, with a total of 17 cases, and one case report describing the disorder (Moore et al., 2006; Soare et al., 2012). However, there is a study of histiocytic sarcoma (HS), as well as reports about haemophagocytic syndrome and haemophagocytic neoplasms, where some included cases had clinicopathological findings and/or disease progression compatible with HHS (Barger et al., 2012; Kato et al., 2013; Skorupski et al., 2007; Stockhaus & Slappendel, 1998; Weiss, 2007). Even though the distinction between HHS, HS and immune-mediated disorders is important with regard to prognosis and treatment, it appears that few patients are diagnosed with HHS, based on available literature.

Previously reported affected breeds include Bernese mountain dogs, golden retrievers, rottweilers, Labrador retrievers, schnauzers, flat-coated retriever and mixed breed dogs (Moore et al., 2006; Soare et al., 2012). Among these dogs, lethargy, inappetence, weight loss, pale mucous membranes, splenomegaly and hepatomegaly were commonly described, which corresponds well with this case (Moore et al., 2006). Reported clinicopathological findings include a regenerative anaemia (94% at initial presentation and eventually 100%), thrombocytopenia (88%), hypoproteinaemia (82%), hypoalbuminaemia (94%), mild prolongation of partial thromboplastin time (70%), hypocholesterolaemia (69%) and mild hyperbilirubinaemia (44%) (Moore et al., 2006). These changes were all seen in the current case, except a prolonged partial thromboplastin time and hyperbilirubinaemia. The explanation for these clinicopathological changes is discussed in depth in the original case series (Moore et al., 2006). The moderate, regenerative anaemia was most likely caused by erythrophagocytosis by neoplastic cells. The extramedullary haematopoiesis observed in the spleen is commonly seen in dogs with haemophagocytic histiocytosis (Moore et al., 2006). The observed increase in erythrocytic precursor cells in the bone marrow corresponds well with regeneration. The mild thrombocytopenia could be a result of neoplastic thrombophagocytosis or thrombocyte consumption by tumour emboli. Hypoalbuminaemia and hypocholesterolaemia could be caused by inflammation since both represent negative acute-phase proteins, as discussed in the previous report (Moore et al., 2006). The moderately increased C-reactive protein also supports the presence of inflammation. Liver insufficiency was less likely since glucose and urea were normal. There was no evident cause for the mild hypoalbuminaemia. Liver insufficiency or protein-losing nephropathy was not suspected, based on blood biochemistry and urine analysis. Protein-losing enteropathy could potentially be the cause, but it was deemed unlikely. At autopsy, the macroscopic findings in the spleen and liver were similar to those previously reported (Moore et al., 2006). Histologically, there were infiltrates of histiocytes with variable atypia, haemosiderin deposits and erythrophagocytosis in the spleen and liver, as well as suspected infiltrates in the lungs and bone marrow. The infiltrates were often accompanied

by foci of extramedullary haematopoiesis. This corresponds well with previous findings (Moore et al., 2006). Fine needle aspirates from the spleen and liver were useful in identifying increased numbers of histiocytes, erythrophagocytosis and haemosiderin deposits.

Immunophenotyping is considered particularly valuable in classifying the lineage of the histiocytes, especially the β 2 integrins CD11/CD18, which are highly regulated amongst canine macrophages and dendritic cells (Danilenko et al., 1992, 1995; Ricklin et al., 2010). Canine histiocytic disorders arising from Langerhans cells and interstitial dendritic cells generally have a high CD11c and a low CD11d expression, whereas disorders arising from macrophages from the red pulp and bone marrow, such as HHS, have a low CD11c and a high CD11d expression (Affolter & Moore, 2002; Allison et al., 2008; Moore, 2014; Moore et al., 1996, 2006; Rossi et al., 2009). In the current case, there were many CD11d + cells in the liver sinusoids and alveolar septa. The full extent of these histiocytic infiltrates was not fully appreciated in the routine H&E stained sections, which was also noted in the previous case series (Moore et al., 2006). Neoplastic histiocytes may have little cellular atypia in HHS, making the distinction between neoplastic and normal cells challenging.

In conclusion, this case report represents the first documented case of HHS in an English setter and the third documented report of HHS in dogs confirmed by immunohistochemistry. Cytology can be a helpful tool for evaluating patients with suspected HHS. However, immunophenotyping is essential to reach a final diagnosis, as neoplastic infiltrates can easily be overseen with routine H&E stained tissues and cytology. Although uncommon, HHS should be considered as a differential diagnosis for regenerative anaemia, both with and without concurrent thrombocytopenia. HHS can easily be misdiagnosed as IMHA or Evan's syndrome, as their clinical picture can be similar.

ACKNOWLEDGEMENTS

The authors thank Associate professor Nina Ottesen (DACVR) for providing diagnostic imaging information for this case report.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Mikael Mathias Kolmannskog Kerboeuf: Formal analysis; Resources; Visualization; Writing-original draft; Writing-review & editing. **Hege Brun-Hansen:** Resources; Supervision; Writing-original draft; Writing-review & editing. **Malin Oscarson:** Resources; Writing-original draft; Writing-review & editing. **Heidi Sjetne Lund:** Resources; Supervision; Writing-original draft; Writing-review & editing.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/vms3.480>.

ORCID

Mikael Kerboeuf  <https://orcid.org/0000-0003-1207-9644>

REFERENCES

- Affolter, V. K., & Moore, P. F. (2002). Localized and disseminated histiocytic sarcoma of dendritic cell origin in dogs. *Veterinary Pathology*, 39(1), 74–83. <https://doi.org/10.1354/vp.39-1-74>
- Allison, R. W., Brunker, J. D., Breshears, M. A., Avery, Anne C., Moore, Peter F., Affolter, Verena K., & Vernau, William (2008). Dendritic cell leukemia in a Golden Retriever. *Veterinary Clinical Pathology*, 37(2), 190–197. <https://doi.org/10.1111/j.1939-165X.2008.00042.x>
- Barger, A. M., Skowronski, M. C., & MacNeill, A. L. (2012). Cytologic identification of erythrophagocytic neoplasms in dogs. *Veterinary Clinical Pathology*, 41(4), 587–589. <https://doi.org/10.1111/j.1939-165x.2012.00472.x>
- Danilenko, D. M., Moore, P. F., & Rossitto, P. V. (1992). Canine leukocyte cell adhesion molecules (LeuCAMs): Characterization of the CD11/CD18 family. *Tissue Antigens*, 40(1), 13–21.
- Danilenko, D. M., Rossitto, P. V., Van der Vieren, M. et al (1995). A novel canine leukointegrin, alpha d beta 2, is expressed by specific macrophage subpopulations in tissue and a minor CD8+ lymphocyte subpopulation in peripheral blood. *The Journal of Immunology*, 155(1), 35–44.
- Kato, Y., Murakami, M., Hoshino, Y. et al (2013). The class A macrophage scavenger receptor CD204 is a useful immunohistochemical marker of canine histiocytic sarcoma. *Journal of Comparative Pathology*, 148(2–3), 188–196. <https://doi.org/10.1016/j.jcpa.2012.06.009>
- Moore, P. F. (2014). A review of histiocytic diseases of dogs and cats. *Veterinary Pathology*, 51(1), 167–184. <https://doi.org/10.1177/0300985813510413>
- Moore, P. F., Affolter, V. K., & Vernau, W. (2006). Canine hemophagocytic histiocytic sarcoma: A proliferative disorder of CD11d+ macrophages. *Veterinary Pathology*, 43(5), 632–645. <https://doi.org/10.1354/vp.43-5-632>
- Moore, P. F., Schrenzel, M. D., Affolter, V. K., Olivry, T., & Naydan, D. (1996). Canine cutaneous histiocytoma is an epidermotropic Langerhans cell histiocytosis that expresses CD1 and specific beta 2-integrin molecules. *American Journal of Pathology*, 148(5), 1699–1708.
- Ricklin, M. E., Roosje, P., & Summerfield, A. (2010). Characterization of canine dendritic cells in healthy, atopic, and non-allergic inflamed skin. *Journal of Clinical Immunology*, 30(6), 845–854. <https://doi.org/10.1007/s10875-010-9447-9>
- Rossi, S., Gelain, M. E., & Comazzi, S. (2009). Disseminated histiocytic sarcoma with peripheral blood involvement in a Bernese Mountain dog. *Veterinary Clinical Pathology*, 38(1), 126–130. <https://doi.org/10.1111/j.1939-165X.2008.00104.x>
- Skorupski, K. A., Clifford, C. A., Paoloni, M. C. et al (2007). CCNU for the treatment of dogs with histiocytic sarcoma. *Journal of Veterinary Internal Medicine*, 21(1), 121–126.
- Soare, T., Noble, P. J., Hetzel, U., Fonfara, S., & Kipar, A. (2012). Paraneoplastic syndrome in haemophagocytic histiocytic sarcoma in a dog. *Journal of Comparative Pathology*, 146(2–3), 168–174. <https://doi.org/10.1016/j.jcpa.2011.05.006>
- Stockhaus, C., & Slappendel, R. J. (1998). Haemophagocytic syndrome with disseminated intravascular coagulation in a dog. *Journal of Small Animal Practice*, 39(4), 203–206.
- Weiss, D. J. (2007). Hemophagocytic syndrome in dogs: 24 cases (1996–2005). *Journal of the American Veterinary Medical Association*, 230(5), 697–701. <https://doi.org/10.2460/javma.230.5.697>

How to cite this article: Kerboeuf M, Brun-Hansen H, Oscarson M, Sjetne Lund H. Case report: Haemophagocytic histiocytic sarcoma in an english setter. *Vet Med Sci*. 2021;7:1154–1158. <https://doi.org/10.1002/vms3.480>