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CASE REPORT

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Clinicopathologic, immunohistochemical, and ultrastructural features of histiocytic sarcoma in a chinchilla (*Chinchilla lanigera*)

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Abstract

A 9-year-old intact female chinchilla (*Chinchilla lanigera*) was presented to a referring veterinarian due to small, multiple cervical nodules that had been rapidly increasing in size and number. Cytology of the nodules revealed sheets of pleomorphic round cells that were morphologically most compatible with histiocytic sarcoma. Histologically, the nodules were fairly demarcated, partially infiltrative, densely cellular neoplasm, and was composed of pleomorphic large round cells arranged in sheets. Special stains for bacteria (Gram stain and Ziehl–Neelsen stain) and fungi (periodic acid-Schiff stain) were all negative. On immunohistochemistry, the neoplastic cells showed strong cytoplasmic positivity for Iba-1 and CD204, but were negative for CD3 and CD20. Transmission electron microscopy failed to detect Birbeck's granules in the cytoplasm of the neoplastic histiocytes. The chinchilla received chemotherapy with lomustine but died spontaneously on day 62 despite treatment. Autopsy with histopathologic examination revealed disseminated histiocytic sarcoma involving the bone marrow, bronchial lymph nodes, nasal cavity, lung, heart, stomach, pancreas, pancreatic lymph nodes, liver, spleen, and kidney. To the best of our knowledge, this is the first report of disseminated histiocytic sarcoma in chinchillas.

KEYWORDS
cytology, disseminated histiocytic sarcoma, histopathology, immunohistochemistry, transmission electron microscopy

1 | INTRODUCTION

Histiocytic proliferative disorders are most commonly reported in dogs and less often in cats and other species. Histiocytic proliferative disorders in dogs include cutaneous histiocytoma, cutaneous Langerhans cell histiocytosis (LCH), reactive histiocytosis (cutaneous or systemic), and histiocytic sarcoma (HS) complex (localized HS, disseminated HS, hemophagocytic HS, and dendritic cell leukaemia) (Hendrick, 2016). HS complex is the most aggressive syndrome in the spectrum of histiocytic diseases and is uniformly fatal. Bernese Mountain Dogs (often with a familial association), Rottweilers, Golden Retrievers, and Flat-Coated Retrievers are pre-disposed breeds to HS complex, but it is not limited to just these breeds and can occur sporadically in any breed (Moore, 2014). HS complex has also been reported in various other domestic species, including cats, cows, horses, rats, hedgehogs, rabbits, and ferrets (Bauchet et al., 2008; Leissinger et al.,

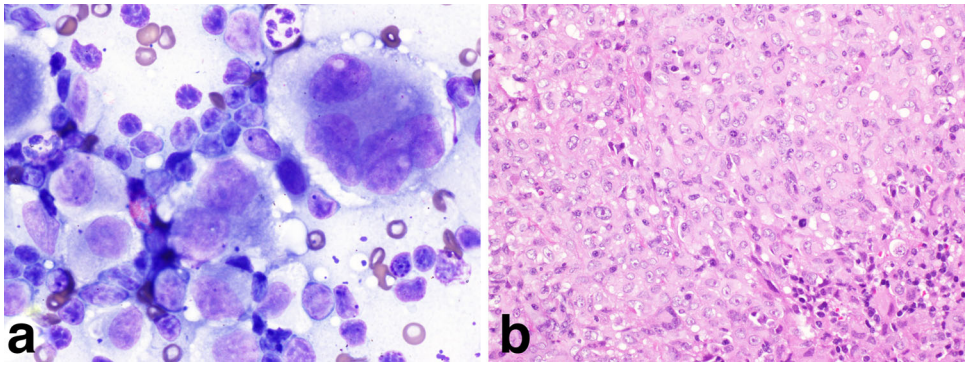

FIGURE 1 Photomicrographs from (a) fine-needle aspirates and (b) a histopathological section of the cervical mass. (a) Many individual pleomorphic round neoplastic cells with oval-to-reniform nuclei with 2–3 prominent nucleoli, fine chromatin, and abundant light blue cytoplasm are noted. These cells demonstrate multiple cytological criteria of malignancy, including moderate to marked anisocytosis, anisokaryosis, frequent karyomegaly, and multinucleation. Intracellular anisokaryosis of a multinucleated giant cell is also noted. In the background, low numbers of small lymphocytes, neutrophils, and eosinophils are observed. Diff-Quick. ×100 objective. (b) Sheets of neoplastic histiocytes with eccentric, oval-to-reniform nuclei with distinct nucleoli, and abundant eosinophilic cytoplasm are noted. Multinucleated giant cells and mitotic figures were observed. Haematoxylin and eosin staining. ×40 objective

2013; Lester et al., 1993; Moore, 2014; Matsuda et al., 2010; Ogihara et al., 2016; Thongtharb et al., 2016). However, to the best of our knowledge, HS complex has not been previously reported in chinchillas.

2 | CASE PRESENTATION

A 9-year-old intact female chinchilla (*Chinchilla lanigera*) (body weight: 0.4 kg) was presented to a referring veterinarian (Nakakaruizawa Animal Hospital, Nagano, Japan) for lethargy, loss of appetite, and laboured breathing. The chinchilla was privately owned and reared indoor. The chinchilla had a 4-year clinical history of multiple chronic nasal and periorbital abscesses associated with malocclusion of the incisors. At initial presentation, the chinchilla was alert and had a clear consciousness, with mild laboured breathing. Physical examination revealed multiple small nodules (diameter, 2–3 mm) located within the cervical areas. The nodules were unresponsive to antibiotic treatment and increased in size (up to 10 mm in diameter) 7 days after the initial presentation. On palpation, the nodules were movable and firm. On hematologic testing on day 10, the chinchilla had mild to moderate leucocytosis ($25.7 \times 10^3/\mu l$, reference interval [RI]: $7.0–12.0 \times 10^3/\mu l$) (Ness, 1999) with mild neutrophilia (segmented neutrophil: $21.2 \times 10^3/\mu l$), without left-shift or toxic changes; these findings were suggestive of chronic inflammation, stress, or physiologic leucocytosis. There was no evidence of anaemia (haematocrit: 41.7%, RI: 39.2%–45.9%) (Ness, 1999). The platelet counts were judged to be adequate on blood smear review. Plasma biochemistry panels revealed mild hyperbilirubinemia (0.9 mg/dl, RI: 0.1–0.6 mg/dl) (Silva et al., 2005), mild azotaemia (44.2 mg/dl, RI: 28.6–42.1 mg/dl) (Silva et al., 2005), mild hyperkalaemia (4.8 mEq/L, RI: 3.4–4.2 mEq/L) (Ness, 1999), and mild hypercalcemia (11.6 mg/dl, RI: 5.4–10.7 mg/dl) (Silva et al., 2005).

Fine-needle aspiration of the cervical nodule was performed, and cytologic smears stained with Diff–Quik stain were submitted to a diagnostic pathology service (Veterinary Specialists Emergency Center, Saitama, Japan) and reviewed by a board-certified veterinary clinical and anatomic pathologist (MGA). The smears had high cellularity and consisted of individual or sheets of neoplastic pleomorphic round cells on a background of small amounts of blood (Figure 1a). Neoplastic cells had central-to-eccentric, oval-to-reniform, irregular large nuclei with 1–2 prominent nucleoli, fine chromatin, and abundant light blue cytoplasm. Moderate to marked anisocytosis, anisokaryosis, a variable nuclear/cytoplasmic ratio, and frequent karyomegaly were observed. Scattered multinucleated giant cells showed marked intracellular anisokaryosis. Frequent mitotic figures with several bizarre mitotic figures were also noted. There was no evidence of erythrophagocytosis. Low numbers of lymphocytes and rare plasma cells, suggesting lymph node population, were also observed. The lymphocytes mostly comprised small, mature lymphocytes with clumped chromatin, and a few medium-to-large–sized lymphocytes with fine chromatin were also present. The cytologic features were most compatible with a diagnosis of HS. The nodules were progressively increased in size (up to 15 mm) and numbers on day 11 of presentation. The nodules were surgically resected, fixed in 10% neutral-buffered formalin and submitted for histopathologic evaluation. The nodules were embedded in paraffin, sectioned at 4-μm thickness, stained with haematoxylin and eosin and reviewed by a board-certified veterinary clinical and anatomic pathologist (MGA).

On histopathologic examination, the nodules were fairly circumscribed, partially invasive, densely cellular neoplasm composed of pleomorphic round cells arranged in sheets (Figure 1b). Neoplastic cells had eccentric, oval-to-reniform nuclei with 1–2 prominent nucleoli and fine chromatin with abundant, slightly granular, eosinophilic cytoplasm. Multinucleated giant cells with 2–5 nuclei per cell were scattered throughout. There were 27 mitotic figures per 10 high-power fields (2.37 mm^2). Staining the sections with special stains (Gram stain, periodic acid-Schiff stain, and Ziehl–Neelsen stain) for bacteria or fungi did not identify any infectious agents (Figure 2a–c).

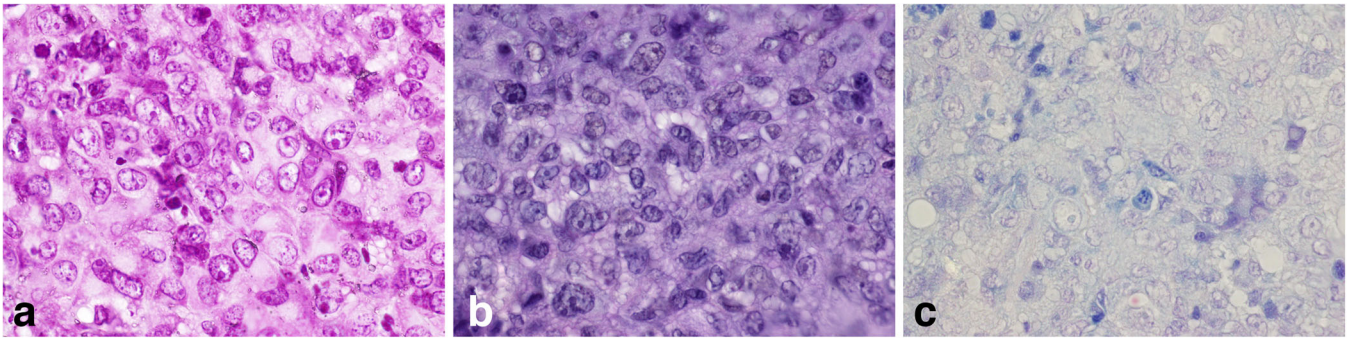

FIGURE 2 Photomicrograph of a histologic section of the cervical mass. (a) Periodic acid-Schiff stain, (b) Gram stain, and (c) Ziehl–Neelsen stain were negative and failed to identify infectious aetiology within the examined sections. ×100 objective

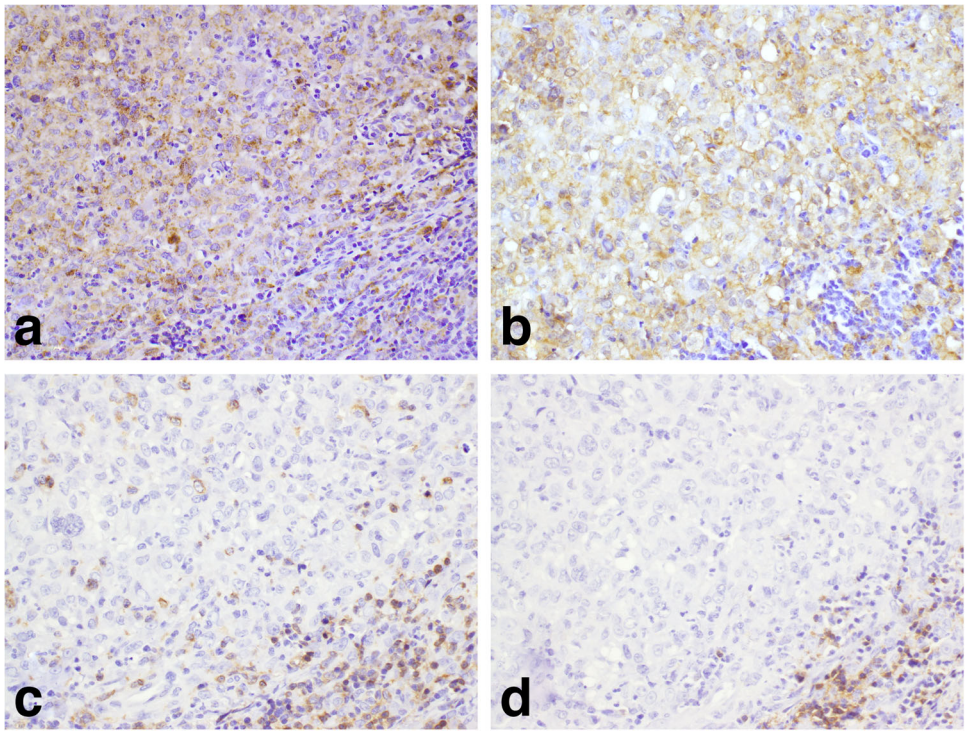

FIGURE 3 Photomicrograph of immunohistochemistry of the cervical mass. (a) More than 90% of neoplastic cells showed strong CD204 positivity (cytoplasmic and membranous) with anti-CD204 antibody. Immunohistochemistry with Mayer's haematoxylin counterstain. ×40 objective. (b) More than 90% of neoplastic cells showed strong Iba-1 positivity (cytoplasmic and membranous) with anti-Iba-1 antibody. Immunohistochemistry with Mayer's haematoxylin counterstain. ×40 objective. (c) No CD3 staining in neoplastic cells. Note CD3 expression in small non-neoplastic lymphocytes around the neoplastic cells. Immunohistochemistry with Mayer's haematoxylin counterstain. ×40 objective. (d) No CD20 staining in neoplastic cells. Note CD20 expression in small non-neoplastic lymphocytes around the neoplastic cells. Immunohistochemistry with Mayer's haematoxylin counterstain. ×40 objective

Immunohistochemical (IHC) staining of the nodule sections for CD3 (rabbit polyclonal, 1:200; Dako, Agilent, Santa Clara, CA), CD20 (rabbit polyclonal, 1:400; Thermo Scientific, Waltham, MA), Iba-1 (rabbit polyclonal, 1:200; Wako, Tokyo, Japan), and CD204 (mouse monoclonal, 1:50, clone no. SRA-E5; Trans Genic, Kobe, Japan) was performed, with a histologic section of the normal lymph node of another chinchilla as a control. IHC staining of the lymph nodes in the control section showed expected positive immunoreactivity for CD3 and CD20 in lymphocytes in the paracortex and germinal centre, respectively, and for Iba-1 and CD204 in macrophages in the medullary sinus and interfollicular cells with dendritic features, respectively. IHC staining was also performed on negative control (Figure S1). More than 90% of the neoplastic cells were strongly immunopositive for Iba-1 and CD204 (membranous and cytoplasmic) and negative for CD3 and CD20 (Figure 3a–d). Based on the histopathologic and immunohistochemical results, a diagnosis of HS was made.

On day 30, a repeated complete blood count revealed persistent moderate leucocytosis ($29.2 \times 10^3/\mu l$, RI: 7.0–12.0 $\times$ $10^3/\mu l$) (Ness, 1999) due to neutrophilia ($24.2 \times 10^3/\mu l$), with no left-shift or toxic change, associated with lymphopenia and eosinopenia, suggesting stress leucocytosis with or without chronic inflammation. Mild thrombocytopenia ($18.9 \times 10^4/\mu l$; RI: 25.4–49.9 $\times$ $10^4/\mu l$) (Ness, 1999) with platelet aggregation was noted and judged to be pseudothrombocytopenia. The chinchilla received chemotherapy with lomustine at 46 mg/m^2 orally on day 30. Leukocyte counts were unchanged on day 37 ($23.5 \times 10^3/\mu l$, RI: 7.0–12.0 $\times$ $10^3/\mu l$) (Ness, 1999), but progressively decreased to the lower end of the RI on day 51 ($7.2 \times 10^3/\mu l$; RI: 7.0–12.0 $\times$ $10^3/\mu l$) (Ness, 1999), and mild toxic change of neutrophils was noted on day 58. Mild, progressive, non-regenerative anaemia (haematocrit: 34.3%, 32.7%, and 29.8% on days 37, 51, and 58, respectively) and mild thrombocytopenia with platelet clumps were noted. No neoplastic histiocytes were seen on the blood smear evaluation. Plasma biochemistry examinations on day 51 showed mild hyperglycaemia (187 mg/dl, RI: 108.4–164.8 mg/dl) (Silva et al., 2005), mild hypoalbuminemia (1.8 mg/dl, RI: 2.4–6.1 mg/dl) (Silva et al., 2005), and mild, persistent hypercalcemia (12.3 mg/dl, RI: 5.4–10.7 mg/dl) (Silva et al., 2005). Ionized calcium levels were not measured.

Despite treatment, the chinchilla died spontaneously on day 62, following which, an autopsy was performed. Histopathological examination was performed using representative tissue samples, including bone marrow, bronchial lymph nodes, nasal cavity, lung, heart, stomach, small and large intestine, pancreas, pancreatic lymph nodes, liver, spleen, kidney, uterus, ovary, cerebrum, and cerebellum. Multifocal-to-coalescing, nodular aggregates of neoplastic histiocytes were observed within the bone marrow (approximately 40% of the section was replaced by the neoplasm), cortex and medulla of the lymph nodes, nasal cavity, interstitium of the lung, atrial septa, gastric lamina propria, pancreas, periportal to random regions of the liver, splenic red pulps, and renal cortex (Figure 4). Osteolysis caused by neoplastic cells was observed within the nasal cavity, adjacent ethmoid plates, and the skull. Concurrent bacterial periodontal and nasal abscesses were also noted. Bone marrow smears from the necropsy showed high cellularity and consisted of erythroid and myeloid precursor cells with complete maturation and mild myeloid left-shift, and scattered megakaryocytes. The myeloid-erythroid ratio was 1:1. Low numbers of well-differentiated plasma cells, small lymphocytes, and mast cells were observed, in addition to large pleomorphic histiocytes. The formalin-fixed lung tissue samples were transferred into 2.5% glutaraldehyde solution and examined by transmission electron microscopy. It revealed the presence of neoplastic cells in the lungs with abundant cytoplasm and oval-to-reniform nuclei containing small clumps of heterochromatin. In the cytoplasm, a large number of cytoplasmic lysosomes were seen, characterized by electron-dense interior granules with a halo beneath a single limiting membrane. However, Birbeck's granules, which are specific to Langerhans cells (LCs), were absent in these neoplastic cells. Interdigitating projections, which are characteristic of LCs, were not observed (Figure 5). A definitive diagnosis of disseminated HS was made based on the electron microscopy findings. To the best of our knowledge, this is the first documented report of disseminated HS in a chinchilla.

3 | DISCUSSION

The classification of histiocytic proliferative diseases is based on the cell of origin and each disorder has a characteristic morphology and anatomic distribution (Hendrick, 2016; Moore, 2014). Canine cutaneous histiocytomas originating from LCs are clinically benign neoplasms that lack cellular atypia. Cutaneous LCH also originates from LCs with mild cellular atypia, in which multiple cutaneous lesions with occasional lymph node, with rarely internal organ involvement. In contrast, canine HS originating from interstitial DCs shows that marked cellular atypia are common and can disseminate to multiple internal organs (Hendrick, 2016; Moore, 2014). Canine hemophagocytic HS, aggressive neoplasm derived from macrophages, is characterized by marked erythrophagocytosis but the neoplastic cells often lack cellular atypia (Hendrick, 2016; Moore, 2014). The cytologic and histologic features as well as the biologic behaviour of HS in our case were similar to those described in other species; it was characterized by large pleomorphic histiocytes with marked cellular atypia and disseminated to multiple organs, suggesting an interstitial dendritic cell (DC) origin.

The use of special stains and immunohistochemical stains was helpful to confirm the diagnosis of HS and exclude granulomatous inflammation, anaplastic lymphoma, and poorly differentiated plasma cell tumour or mast cell tumour (Hendrick, 2016). HS originates from interstitial DCs; therefore, neoplastic cells express CD1 and CD11c (Moore, 2014). These markers provide the best results on frozen tissues but are unstable for use with paraffin-embedded tissues. Therefore, anti-ionized calcium-binding adapter molecule-1 (Iba-1) and anti-CD204 (anti-human macrophage scavenger receptor) antibodies, which are available for formalin-fixed tissues (Imai et al., 1996; Ito et al., 1998, Kato et al., 2013), were used as markers for the monocytic and histiocytic lineages in this case. CD204 is a major macrophage receptor and the monoclonal antibody for CD204 recognizes canine tissue resident macrophages (i.e., alveolar macrophages, Kupffer cells, and splenic macrophages) and has been used to confirm HS in dogs, cats (Hirabayashi et al., 2020), rabbit (Ishimori et al., 2017), and hedgehog (Son et al., 2020). However, epidermal LCs are reported to be negative for CD204 (Hirabayashi et al., 2020; Kato et al., 2013; Tomokiyo et al., 2002). Iba-1 is a microglia/macrophage-specific calcium-binding protein and a pan-macrophage marker. Its expression has been reported in canine cutaneous histiocytoma, reactive histiocytosis (Pierezan et al., 2014), and HS in various species, including dog, rabbit (Ishimori et al., 2017), and hedgehog (Son et al., 2020). Positive staining on the control section of another chinchilla supported the cross-reactivity of these markers in chinchillas, and immunohistochemistry was helpful to confirm the diagnosis of HS of interstitial DC origin.

Transmission electron microscopy findings further supported the interstitial DC origin of this neoplasm. In humans, LCs are characterized by the presence of Birbeck's granules in their cytoplasm, which distinguish them from interstitial DCs. Previous studies have shown that Birbeck's granules are present in the LCs of humans and various animals, including mice (Merad et al., 2008), pigs (Nfon et al., 2008), and cats (Saint-Andre et al., 1997), but are absent in dogs (Moore, 2014). In this case, the lack of Birbeck's granules suggests a possible DC origin; however, this result must be interpreted with future studies of

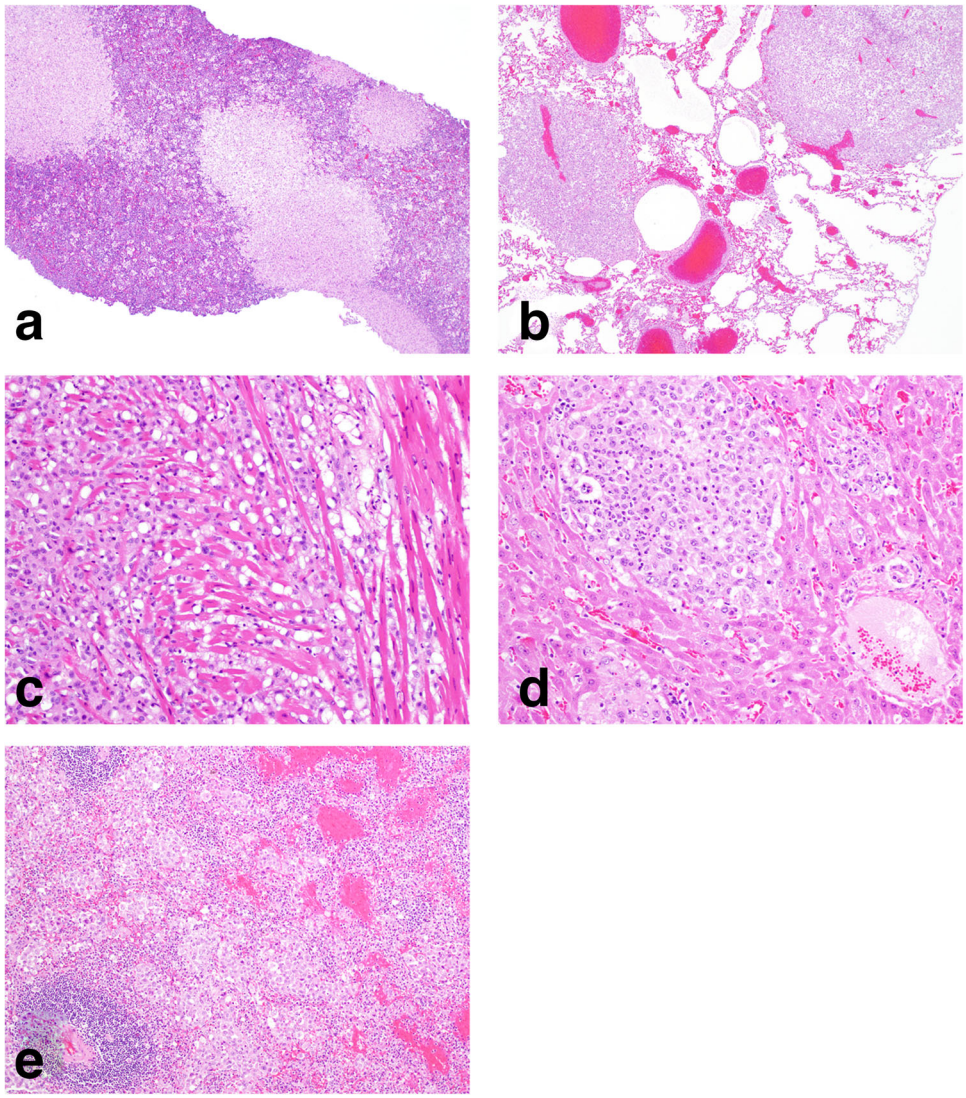

FIGURE 4 Photomicrographs of histologic sections, haematoxylin, and eosin stain. (a) Bone marrow. Approximately 40% of the bone marrow is replaced and infiltrated by neoplastic cells. ×4 objective. (b) Lung. Neoplastic cells infiltrate and efface the normal tissue architecture and form multifocal nodular aggregates. ×4 objective. (c) Heart. The cardiomyocytes are separated by neoplastic cellular infiltrates. ×20 objective. (d) Liver. The periportal, mid-zonal, and centrilobular hepatic cords are multifocally and randomly infiltrated by nodular aggregates of neoplastic histiocytes. ×20 objective. (e) Spleen. The red pulp of the spleen has multifocal-to-coalescing small nodular aggregates of neoplastic histiocytes. ×10 objective

chinchillas' LCs. To the best of our knowledge, there is no previous study on Birbeck's granules in LCs in chinchillas, and post-mortem autolysis might have prevented the detection of Birbeck's granules in this case.

HS is a highly aggressive neoplasm and systemic chemotherapy with CCNU (lomustine) is reported to be the most effective with response rate of 46%, and the median survival time of responders was 172 days in dogs (Skorupski et al., 2007; Clifford et al, 2012). In our case, despite chemotherapy, the patient died spontaneously 62 days after the initial presentation (1 month after chemotherapy initiation), suggesting HS in chinchillas also has a grave prognosis, similar to that in dogs.

In addition, thrombocytopenia ($<10 \times 10^4$ platelets/μl) and hypoalbuminemia have been reported to be negative prognostic factors and were predictive of <1-month survival in dogs (Skorupski et al., 2007). It remains unknown whether a similar trend can be seen in chinchillas, and platelet counts, in this case, were adequate at day 30 and never decreased below 10×10^4 /μl on blood smears. In contrast, hypoalbuminemia was observed in this case. The plasma albumin level was at the lower end of the RI (2.4 mg/dl, RI: 2.4–6.1 mg/dl) (Silva et al., 2005) at day 30 and decreased to 2.4 and 1.8 mg/dl on days 30 and 51, respectively, which may be associated with decreased production in the liver due to inflammatory cytokine stimulation, neoplastic infiltrates in the liver, chemotherapy-related hepatotoxicity, decreased intestinal absorption, and/or increased renal loss from neoplastic infiltrates in the gastrointestinal tract and kidney. Persistent mild hypercalcemia was noted on days 10 and 51 in this case. Hypercalcemia is an uncommon (3%) finding in canine HS (Moore, 2014). In the present case, it may also have been related to neoplastic osteolysis found in the

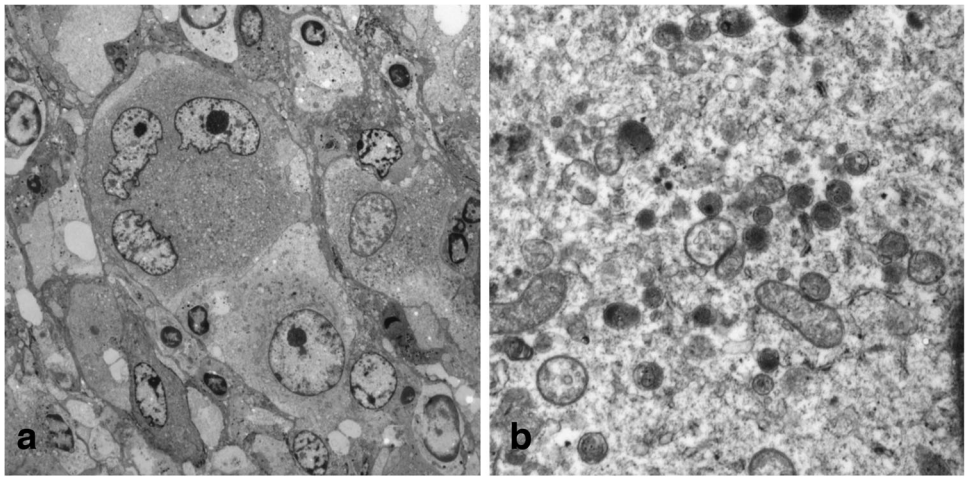

FIGURE 5 Transmission electron micrographs of neoplastic histocytes in the lungs. Neoplastic cells have abundant cytoplasm, oval-to-reniform nuclei with clumps of heterochromatin, and many intracytoplasmic electron-dense granules with a single membrane and halo (lysosomes). No Birbeck's granules, characteristic of Langerhans cells, are noted. (a: ×1200, b: ×15000)

nasal cavity, ethmoid plate, and skull. Moreover, neoplastic infiltrates in the renal cortex may have resulted in decreased urinary excretion due to increased calcium bound to citrate or phosphate. Increased ionized calcium levels due to parathyroid-related peptide (PTH-rP) production have been commonly reported in lymphomas occurring in domestic animals; however, a validated measurement of ionized calcium and PTH-rP is not commercially available in this species.

The cause of progressive anaemia in our patient was likely due to decreased production resulting from neoplastic infiltrates, which was evident in the histologic sections. The bone marrow smears contained only a few neoplastic cells, and detecting neoplastic cells can be difficult on cytology when tumour cells are localized or multifocal. Mild toxic changes in the peripheral blood at day 58 and left-shifted myeloid precursor cells in the bone marrow at the necropsy (day 62) were due to accelerated bone marrow production, likely secondary to severe and chronic bacterial periodontal and nasal abscesses in this case. Bone marrow hypoplasia due to chemotherapy was not evident and marrow cellularity was normal-to-increased (100%) in this case, suggesting that administration of a higher dosage of lomustine could be considered for future cases.

Further investigation to establish a definitive classification of histiocytic proliferative disorders with validated different antibodies will be warranted in chinchillas. To the best of our knowledge, this is the first documented report of disseminated HS in a chinchilla.

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AUTHOR CONTRIBUTIONS

Formal analysis, *investigation*, *validation*, *visualization*, *and writing-original draft*: Kaoru Enomoto. *Formal analysis*, *investigation*: Chihiro Tsutsumitani. *Conceptualization*, *data curation*, *formal analysis*, *investigation*, *supervision*, *and writing-review & editing*: Midori Goto Asakawa.

PEER REVIEW

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SUPPORTING INFORMATION

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