



NOTE

Wildlife Science

Clinical management and outcome of four-toed hedgehogs (*Atelerix albiventris*) with histiocytic sarcoma

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ABSTRACT. Four-toed hedgehogs presented bloody stool and loss of appetite. Integumental masses were observed in two of the four cases. Intraabdominal masses were observed on radiographs and ultrasonography in the remaining two cases. The masses were surgically removed from all four cases. All samples were histologically and immunohistochemically consistent with histiocytic sarcoma (HS). At the time of surgery, 3 of 4 cases had grossly recognized metastatic/disseminated lesions. Survival time was 48 days, 64 days, and 113 days, respectively, and the remaining case is currently alive (at Day 207). The present report describes the clinical management and outcome of hedgehogs that were diagnosed with HS.

KEY WORDS: *Atelerix albiventris*, four-toed hedgehog, histiocytic sarcoma

Four-toed hedgehogs (*Atelerix albiventris*) have become popular pets in many countries, and the database concerning disease in these animals is growing [3, 8]. This species is known to commonly develop neoplastic diseases, and necropsy reports have indicated a tumor incidence of 29–51.5% [4, 12] with 85% of the neoplastic diseases being malignant [12]. Neoplastic disease is the primary cause of death in four-toed hedgehogs, accounting for 35.9% of all causes of death in captive animals [11]. To obtain appropriate prognostic evaluations and radical treatment opportunities for neoplastic disease in four-toed hedgehogs, accurate and early diagnosis is essential [4].

Histiocytic sarcoma (HS) is an interstitial dendritic cell- or macrophage-derived malignant tumor [7]. Histiocytic sarcoma is known to develop commonly in dogs, although the incidence is low in cats [7]. Hematopoietic tumors account for 11% of all tumors in four-toed hedgehogs and are the second most frequently occurring group of tumors [4, 12]. Development of lymphoma and leukemia are relatively well known [12], but reports on HS are limited. Development of skin, brain, and disseminated HS has been reported, but only one case each [6, 9, 12] and the only detailed reports have been based on postmortem diagnoses. The present report is the first to present the histopathological antemortem diagnosis and surgical resection treatment in four four-toed hedgehogs with HS, including detailed descriptions of clinical findings.

Data on signalment, clinical findings, and outcome of each hedgehog are summarized in Table 1.

Case 1: A 2.8-year-old, 427-g spayed female four-toed hedgehog was brought into a clinic with a chief complaint of bloody stool. The hedgehog was alert with normal activity and appetite. Medical history included diagnosis of endometrial polyps. On Day 3, the hedgehog underwent induction and maintenance of anesthesia with 3% isoflurane inhalant (ISOFLURANE Inhalation Solution; Pfizer, Tokyo, Japan) and oxygen (2 l/min), and detailed examination was performed under general anesthesia. Since X-ray and ultrasound examinations revealed mass lesions in the abdominal cavity, an exploratory laparotomy was performed on Day 6. Following intramuscular injection of a mixture of 0.25 mg/kg midazolam (Dormicum inj.; Astellas Pharma, Tokyo, Japan) and 0.25 mg/kg butorphanol (Vetorphale; Meiji Seika Pharma, Tokyo, Japan), anesthesia was induced with 2% isoflurane and oxygen (2 l/min) via an anesthetic chamber and maintained at 1–3% with a face mask. Vascular access was secured in the lateral saphenous vein of the hind leg using a 26-G indwelling needle, and continuous drip of Ringer's lactate solution (Solulact; Terumo Corp., Tokyo, Japan) was supplied at 10 ml/kg/hr. Abdominal midline incision revealed multiple indurated masses at the mesenteric lymph nodes (Fig. 1). One of the masses was adjacent to the ileum, and ileal wall degeneration was detected on visual inspection and palpation. To avoid future development of intestinal obstruction, end-to-end anastomosis of the ileum was performed after resecting the ileum along with one of the masses. Biopsy of the omentum was performed at the same time. The surgical incision was closed using a conventional protocol. Histopathological examination revealed round cell infiltration in all layers of the ileum from lamina propria, submucosa, muscle layers, to serosa (Fig. 2). Tumor cells had distinct cell

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Table 1. Signalment, clinical findings and outcome of the animals

Case	1	2	3	4
Age (year)	2.8	3.7	2.7	3.1
Body weight (g)	427	598	341	704
Sex	Spayed female	Female	Male	Spayed female
Clinical signs	Bloody stool	Anorexia, decreased activity	Mass formation at left neck	Subcutaneous mass at right neck
Physical examination findings	Palpable mass in the upper right abdomen in the abdominal cavity	Palpable mass in the upper left abdomen in the abdominal cavity	Indurated and immobile subcutaneous mass (1.5 × 2.0 cm) in the left neck	Soft subcutaneous mass (2.0 × 2.0 cm) in the right neck
Thoracic and abdominal radiographic findings	Abdominal cavity mass, mild retention of gastrointestinal gas	Abdominal cavity mass, enhanced radiopaque lung field	No abnormalities	Not done
Thoracic and abdominal ultrasonographic findings	Multiple hypoechoic oval-shaped masses	Mass lesions with a mix of hypo- and hyperechoic patterns in the upper left abdomen in the abdominal cavity, cystic lesions in both ovaries	No abnormalities	No abnormalities
Complete blood count	High PCV (45%; reference value, 29–43%) From Ivey <i>E et al.</i> [5]	No abnormalities	No abnormalities	Mild anemia (28%)
Serum biochemical analyses	Moderate hypoalbuminemia (1.6 g/dl; reference value, 2.5–3.2 g/dl) [5], moderate hyperglobulinemia (4.2 g/dl; reference value, 2.2–3.2 g/dl) [5], mild hypercalcemia (10.7 mg/dl; reference value, 7.4–10.2 mg/dl) [5], mild hypophosphatemia (2.8 mg/dl; reference value, 3.4–7.2 mg/dl) [5], mildly low BUN (12 mg/dl; reference value, 18–36 mg/dl) [5]	Mild hyponatremia (130 mEq/l; reference value, 132–150 mEq/l), moderate hyperkalemia (6.7 mEq/l; reference value, 3.9–5.9 mEq/l), mild hyperglobulinemia (3.7 g/dl), mild hypercalcemia (10.8 mg/dl) [5]	Mild hypoalbuminemia (2.4 g/dl), moderate hyperglobulinemia (4.7 g/dl), mild hyperproteinemia (7.1 g/dl; reference value, 5.1–6.5 g/dl) [5], mild hypophosphatemia (3.1 mg/dl; reference value, 3.4–7.2 mg/dl) [5]	Mild hypoalbuminemia (1.9 g/dl), mild hyperglobulinemia (3.9 g/dl), mild hyponatremia (127 mEq/l), mild hyperglycemia (125 mg/dl; reference value, 59–119 mg/dl) [5]
Cytological examination of mass lesion	Not done	Not done	Few neutrophils and lymphocytes	Large round cells with moderate atypia
Outcome	Died on day 48	Currently alive (day 207)	Died on day 64	Died on day 113
Necropsy findings	Not done	Not done	Not done	Metastatic lesions of histiocytic sarcoma observed in subcutaneous tissue in the right neck, base of the heart, and left neck, lung, liver, spleen, pancreas, mesenteric lymph nodes, and right humerus

BUN, blood urea nitrogen; PCV, packed cell volume.

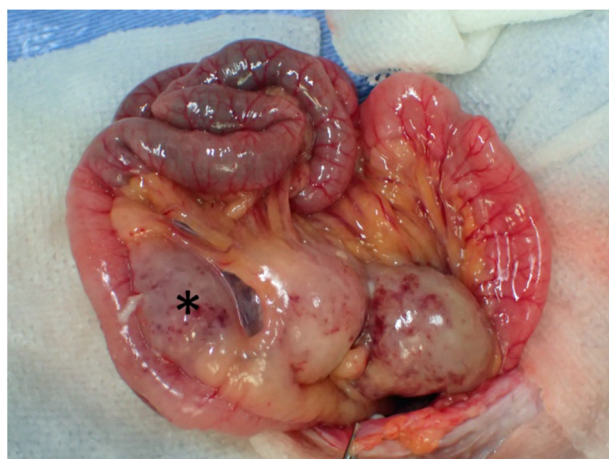


Fig. 1. Intraabdominal mass in Case 1. Enlargement of multiple mesenteric lymph nodes is observed. Only the mass adjacent to the ileum (*) was resected together with the ileum.

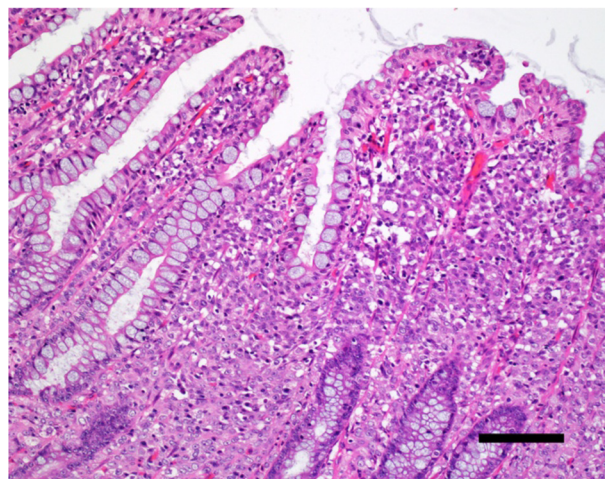


Fig. 2. Histological findings of the mass in Case 1. Diffuse infiltration of tumor cells in the lamina propria of the intestine. Hematoxylin and eosin staining. Bar=50 μ m.

borders and had a small amount of eosinophilic cytoplasm. The nucleus was small and round, and contained coarsely stippled chromatin and with distinct nucleoli. Atypia was moderate and 10 mitoses per 10 high-power fields were observed. Similar tumor cells were also observed at the mesenteric nodular lesion. Immunohistochemically, tumor cells were CD20-negative, CD3-negative, and Ionized calcium binding adapter molecule 1 (Iba-1)-positive, leading to the diagnosis of HS (Fig. 3). The hedgehog was administered enrofloxacin (5 mg/kg, SC, q 24 hr, Enrofloxacin injection 25 KS for dogs and cats; Kyoritsu Seiyaku Corp., Tokyo, Japan), piperacillin (20 mg/kg, SC, q 12 hr, Piperacillin injection Nichiiko; Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), buprenorphine (0.02 mg/kg, SC, q 12 hr, Lepetan injection; Otsuka Pharmaceutical, Tokyo, Japan), prednisolone (2 mg/kg, SC, q 24 hr, Prednisolone injection KS; Kyoritsu Seiyaku Corp.), famotidine (1 mg/kg, SC, q 12 hr, Famotidine injection Sawai; Sawai Pharmaceutical, Osaka, Japan), and lactated Ringer's solution (25 ml/kg, SC, q 24 hr) under hospitalization. In addition, after 36 hr of postoperative fasting, gavage every 8 hr (Recovery Period Support; Royal Canin Japon, Tokyo, Japan) was started from Day 8. On Day 9, sodium amidotrizoate meglumine solution (2.5 ml/kg, Gastrografin Oral Enema; Bayer Pharmaceuticals, Osaka, Japan) was administered orally to perform an upper gastrointestinal series. Since flaccid loops of small intestine were visualized with contrast agent and decreased gastrointestinal motility was suspected, metoclopramide (0.5 mg/kg, SC, q 12 hr, Primperan injection; Astellas Pharma, Tokyo, Japan) and mosapride citrate (1 mg/kg, PO, q 12 hr; Pronamide tablet; DS Pharma Animal Health, Osaka, Japan) were added from Day 10. The hedgehog was able to feed independently on Day 10 and passed stool (albeit as diarrhea) on Day 11, and was subsequently discharged. Prescriptions at discharge were: amoxicillin (20 mg/kg, PO, q 12 hr, Amoxiclear tablets; Kyoritsu Seiyaku Corp.), enrofloxacin (5 mg/kg, PO, q 12 hr, Reneval; Zoetis, Tokyo, Japan), famotidine (1 mg/kg, PO, q 12 hr, Famotidine tablets, Takeda Pharmaceuticals Co., Osaka, Japan), metoclopramide (0.5 mg/kg, PO, q 12 hr, Primperan tablets; Astellas Pharma), mosapride citrate (1 mg/kg, PO, q 12 hr), and prednisolone (2 mg/kg, PO, q 24 hr; prednisolone tablets, Takeda Pharmaceuticals Co., Osaka, Japan). After discharge, activity, appetite and diarrhea temporarily improved, but activity and appetite gradually decreased and soft stool reappeared. In addition to the above medications, anti-diarrhea medication was given; but symptoms did not improve and the hedgehog died on Day 48.

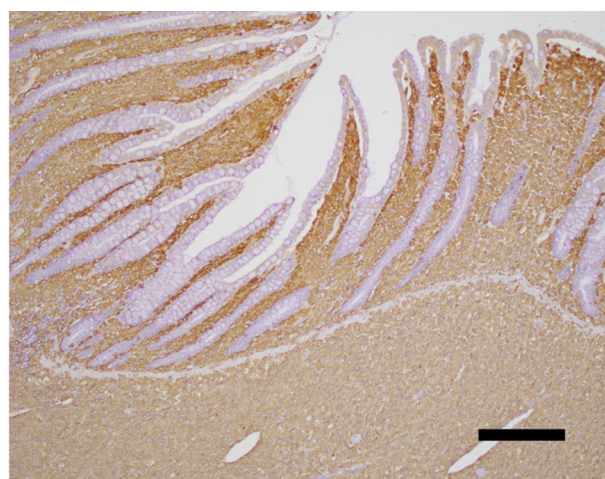


Fig. 3. Immunohistochemical findings of tumor tissue in Case 1. Tumor cells are Iba-1-positive. Counterstaining hematoxylin, Bar=200 μ m.

Case 2: A 3.7-year-old, 598-g female four-toed hedgehog was brought into a clinic with chief complaints of anorexia and decreased activity. Using the same isoflurane inhalation anesthesia protocol used in Case 1, a detailed examination was performed under general anesthesia. Since X-ray and ultrasound examinations revealed a mass lesion in the abdominal cavity, an exploratory laparotomy was performed on Day 2. Perioperative anesthetic management was performed in the same manner as for Case 1. An abdominal midline incision revealed a giant, mottled pink-and-white mass lesion of unknown origin that adhered to the spleen,

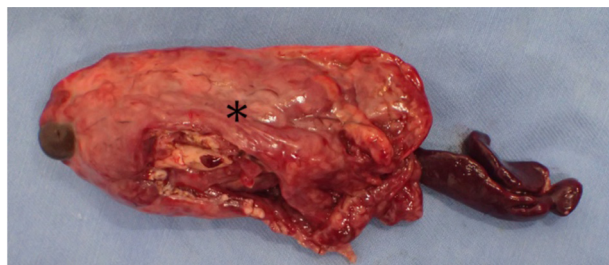


Fig. 4. Intraabdominal mass (*) extracted from Case 2.

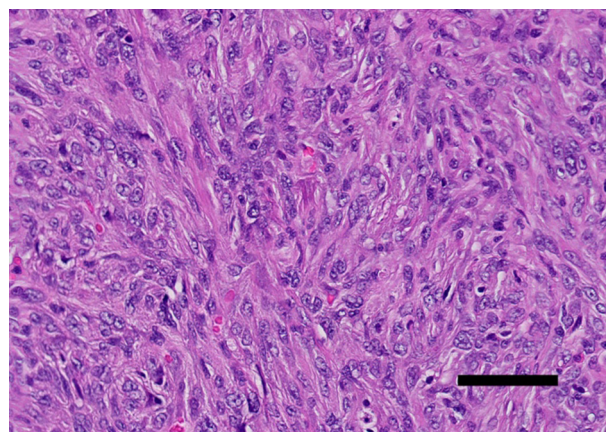


Fig. 5. Histological findings of the mass in Case 3. The tumor is composed of interweaving spindle cells. Tumor cells display moderate atypia. Hematoxylin and eosin staining, Bar=50 μ m.

pancreas, and stomach at the ventral left upper abdomen of the caudal stomach. After detaching the mass from the stomach, the pancreas was partially resected and the spleen was completely resected, thereby removing the mass (Fig. 4). Histopathological and immunohistochemical examination revealed tumor tissue proliferation that was essentially the same as that in Case 1, leading to a diagnosis of HS. Tumor cells were also observed at the spleen, pancreas, ovary, and uterus. The hedgehog was administered enrofloxacin (5 mg/kg, SC, q 24 hr), buprenorphine (0.02 mg/kg, SC, q 12 hr), meloxicam (0.2 mg/kg, SC, q 24 hr) and lactated Ringer's solution (30 ml/kg, SC, q 24 hr) under hospitalization. The hedgehog showed satisfactory postoperative general condition, and was discharged on Day 5 with prescriptions of enrofloxacin (5 mg/kg, PO, q 24 hr) and meloxicam (0.2 mg/kg, PO, q 24 hr, Metacam Chewable Tablets, 1.0 mg; Boehringer Ingelheim Vetmedica, Japan, Tokyo, Japan). On Day 19, sutures were removed and treatment was concluded. Medications have not been given thereafter. On Day 207 (the time of this report), the general physical condition of the hedgehog is satisfactory and X-ray and ultrasound examinations have not detected any recurrences of neoplastic lesions.

Case 3: A 2.7-year-old, 341-g male four-toed hedgehog was brought into a clinic with a chief complaint of a neck mass. The hedgehog was alert with normal activity and appetite. Using the same isoflurane inhalation anesthesia protocol used in Case 1, detailed examination was performed under general anesthesia. A subcutaneous indurated immobile mass (2.0 \times 1.5 \times 1.5 cm) at the left neck bottom was observed. Cytological examination revealed a small number of neutrophils and lymphocytes, but results were nondiagnostic. On Day 6, the neck mass was resected. Perioperative anesthetic management was performed similarly to Case 1. The mass had adhered to the left external jugular vein and was difficult to detach, so the left external jugular vein was clamped with a hemoclip (Euroclip; Kawasaki Seibutsu Kagaku Research Institute, Tokyo, Japan) and the whole blood vessel was extracted. At the same time, the salivary gland adherent to the caudal side of the mass and the enlarged left cervical lymph node were also extracted. Histopathological examination revealed a poorly circumscribed invasive mass from the dermis to the subcutaneous tissue, composed of interweaving spindle cells (Fig. 5). Immunostaining showed the tumor cells were CD20-negative, CD3-negative, and Iba-1-positive, leading to a final diagnosis of HS. In addition, metastatic lesions were observed in the lymph node extracted at the same time. Postoperative medications during hospital stay were the same as those in Case 2. The hedgehog presented left facial edema for a short period postoperatively, but exhibited a satisfactory general condition, and was discharged on Day 9 with prescriptions of enrofloxacin (5 mg/kg, PO, q 24 hr) and meloxicam (0.2 mg/kg, PO, q 24 hr). Facial edema improved over time and sutures were removed on Day 22. However, decreased activity and appetite were observed from Day 31 and X-ray and ultrasound examinations under isoflurane inhalation anesthesia on Day 43 revealed enhanced radiopacity in the lung and multiple hypoechoic lesions in the left kidney, spleen, and liver. Moreover, ultrasonography through the surgical wound at the neck detected a 0.63 \times 1.04 cm hypoechoic lesion. A soft mass was detected on palpation of the left maxillary cheek and cytological examination revealed neutrophils as well as numerous large, round cells. Based on these findings, tumor recurrence and metastasis to multiple organs were suggested. The hedgehog presented abnormally rapid respiration from Day 50 and was administered additional theophylline (10 mg/kg, PO, q 12 hr, theophylline sustained-release tablet; Nichi-Iko Pharmaceutical, Toyama, Japan), but died on Day 64 due to dyspnea.

Case 4: A 3.1-year-old, 704-g spayed female four-toed hedgehog was brought into a clinic with a chief complaint of subcutaneous mass formation at the right neck. The hedgehog was alert with normal activity and appetite. Medical history included a diagnosis of cystic endometrial hyperplasia. Using the same isoflurane inhalation anesthesia protocol used in Case 1, detailed examination was performed under general anesthesia. A soft, sessile mass was observed at the right neck and cytological examination revealed large round cells with moderate atypia. Biopsy was consequently performed using a biopsy gun (SuperCore Biopsy Instrument 16ga \times 9 cm; Argon Medical Devices, Frisco, TX, U.S.A.). The mass at the right neck was diagnosed as sarcoma according to histopathological examination, and was resected on Day 10. Perioperative anesthetic management was

performed similarly to Case 1. An incision to the neck skin and detachment of subcutaneous tissue revealed a mass in the deep layer of the neck and adherent to the right external and internal jugular veins. The neck mass was subsequently detached and removed. In addition, the salivary gland was also resected at the same time, as it was compressed and displaced by the mass. Histopathological examination showed tumor tissue proliferation that was essentially the same as that in Cases 1 and 2, but with more marked tumor cell atypia. Immunostaining showed tumor cells to be CD20-negative, CD3-negative, and Iba-1-positive, leading to a definitive diagnosis of HS. The medications given during postoperative hospital stay were the same as those in Case 2. The hedgehog recovered well postoperatively and was discharged on Day 13 with a prescription of enrofloxacin (5 mg/kg, PO, q 24 hr). On Day 20, sutures were removed and the absence of local recurrence was confirmed with palpation. This concluded the treatment. On Day 78, the hedgehog was brought in due to a recurrence of the mass at the right neck. Examination under isoflurane inhalation anesthesia revealed a recurrent mass (2.04 × 1.74 cm) at the right neck that was firmly fixed to the neck muscle. Ultrasound examination detected a 0.63 × 0.75-cm, hypoechoic nodule surrounded by hyperechoic areas in the liver and a 0.52 × 0.86-cm hypoechoic lesion on the cranial side of the heart, and metastasis was suspected. Enrofloxacin (5 mg/kg, PO, q 24 hr), prednisolone (0.5 mg/kg, PO, q 24 hr), and famotidine (1 mg/kg, PO, q 12 hr) were prescribed and the hedgehog underwent follow-up examination, but the mass at the neck continued to enlarge. Due to intermittent decreases in appetite, the hedgehog was fed via gavage (Recovery Period Support). The hedgehog died due to sudden hemoptysis on Day 113 during follow-up examination. Necropsy revealed a white, indurated mass continuing from the right neck to the cranial thoracic cavity and multifocal pale yellow nodular lesions in the liver (Fig. 6). Histopathologically, metastatic lesions were confirmed in masses of the subcutaneous tissue of the right neck, base of the heart, left neck, lung, liver, spleen, pancreas, mesenteric lymph nodes, and right humerus.

Differential diagnoses of HS include other round cell tumors such as lymphoma, and diagnosis is thus challenging from histopathological examination alone. Definitive diagnosis requires immunostaining [9]. Previous reports on HS in four-toed hedgehogs have also stated the utility of immunostaining including CD3 (as a T lymphocyte marker), CD20 (as a B lymphocyte marker) and Iba-1 (as a histiocytic marker) [9, 10]. This was also the case in our report, where HS was definitively diagnosed in all cases with anti-Iba-1 antibody immunostaining in addition to histological examinations. Lymphoma was ruled out in all cases due to negative against both lymphocytic markers used. The tumor tissue in Case 3 primarily comprised proliferating spindle cells, requiring distinction from sarcoma derived from stromal tissue (soft-tissue sarcoma). Previous reports in dogs have noted that HS presents with various histological appearances, as a “histiocytic-spindle-pleomorphic subtype”, leading to definitive diagnosis from immunohistochemical examinations [1]. The tumor cells in Case 4 displayed a poorly differentiated morphology, and immunohistochemical examinations were useful for identifying the origin of tumor cells. These findings suggested that the morphology of HS based on histopathological images varies widely in four-toed hedgehogs.

Canine HS is known to occur in various sites, including the spleen, lungs, lymph nodes, bone and joints, skin and subcutaneous tissues, liver, central nervous system, oral mucosa, and kidneys [2, 13]. HS in the present report appeared at various sites including the subcutaneous tissue, peritoneal fat, and mesenteric lymph node, suggesting that this disease may present similar properties in four-toed hedgehogs compared to dogs. Laboratory test results were nonspecific for serum biochemistry analysis and complete blood count, but palpation and X-ray and ultrasound examinations could easily detect the mass diagnosed as HS, leading to the decision of surgical treatment. The utility of these examinations in cases of HS in four-toed hedgehogs was verified. Cytodiagnostic examination revealed large round cells suggestive of HS at the time of recurrence in Case 3 and the first visit in Case 4, indicating a certain level of usefulness. On the other hand, because obvious atypical cells could not be obtained at initial onset in Case 3, the importance of definitive diagnosis through histopathological examination and immunostaining was highlighted.

Two types of canine HS are known: localized histiocytic sarcoma (LHS), where lesions are localized; and disseminated histiocytic sarcoma (DHS), where lesions form systemically [7]. Whether DHS develops as a result of distant metastasis of a primary mass or is essentially a multicentric systemic disease is unknown [14], but early and widespread metastasis occurs in the early stage even in LHS [2, 14]. Based on general physical examination, imaging studies, and histopathological examination at diagnosis in our report, Cases 1 and 2 were considered to represent DHS while Cases 3 and 4 were considered as LHS. In Case 3, LHS had likely metastasized to the local lymph node. The prognosis of dogs with HS is poor, with an overall median survival ranging from 43 to 170 days, and among these cases, DHS is reported as a poor prognostic factor [2, 14]. According to Dervisis *et al.*, the median survival of dogs with LHS and DHS was 398 days and 78 days, respectively [2]. They also stated that median survival was significantly shorter in dogs with confirmed lymph node metastasis [2]. In our report, clear prognostic factors were difficult to determine due to the small number of cases. However, Cases 1–3 had already presented dissemination or metastasis at the time of diagnosis and Case 4 ultimately showed metastasis to multiple organs, indicating the high probability that HS in four-toed hedgehogs presents a similar pathology to HS in dogs and suggesting that the prognosis is poor. Moreover, chemotherapy with

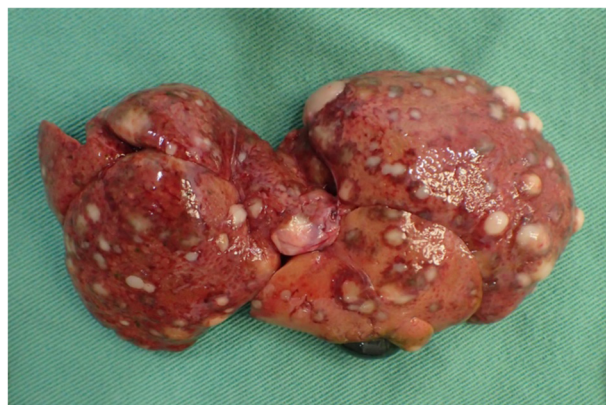


Fig. 6. Gross findings of the liver at necropsy for Case 4. Multifocal pale yellow nodules in the liver.

Iomustine in addition to surgical resection is recommended in canine HS, and this treatment method has resulted in a significant extension of survival [2, 14].

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