Histiocytic sarcoma in miniature schnauzers: 30 cases

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OBJECTIVES: To summarise the clinical presentation and outcomes in a series of miniature schnauzers diagnosed with histiocytic sarcoma.

MATERIALS AND METHODS: Retrospective review of medical records of miniature schnauzers diagnosed with histiocytic sarcoma between 2008 and 2019 at two referral centres in the UK. Signalment, clinical signs at initial presentation, imaging results and clinico- and histopathological findings, treatment type and outcome were recorded. Progression-free survival and overall survival time were calculated.

RESULTS: Thirty dogs were included. Twenty-four of 29 dogs undergoing imaging of the thorax had lung and/or mediastinal involvement. The median overall survival time for dogs that were not euthanased within 3 days of diagnosis was 117 days (range 10 to 790). Three dogs underwent surgery; 13 received treatment with lomustine as a sole therapy - with partial responses documented on imaging in five of six dogs and 11 of 13 showing clinical improvement.

CLINICAL SIGNIFICANCE: Histiocytic sarcoma should be considered as a differential diagnosis for miniature schnauzers with pulmonary masses. Although responses to treatment were common, they were usually short-lived because of the aggressive nature of the disease.

INTRODUCTION

Canine histiocytic tumours encompass a group of neoplasms with diverse cellular origins and different biological behaviours. Histiocytic sarcoma (HS) is a malignant neoplasm with an aggressive clinical course. Three forms of HS have been recognised, based on the clinical presentation and cellular origin of the tumour: localised, disseminated and haemophagocytic (Moore et al. 2006, Fulmer & Mauldin 2007, Skorupski et al. 2007, Dervisis et al. 2017). Localised and disseminated HS originate from dendritic cells, while haemophagocytic HS originates from macrophages. Localised HS describes neoplastic histiocytic cells that can arise from various tissues, including skin/subcutaneous tissue, skeletal muscle, joint/bone, liver, spleen, lymph node, lungs, mediastinum, central nervous system and eye. (Craig et al. 2002, Naranjo et al. 2007, Skorupski et al. 2007, Klahn et al. 2011, Kagawa et al. 2015, Mariani et al. 2015, Dervisis et al. 2017, Marlowe et al. 2018) while the disseminated form is characterised by multiorgan involvement.

Certain breeds appear either predisposed or have increased frequency of HS -most notably Bernese mountain dogs, flat-coated retrievers and Rottweilers. While disseminated HS appears most frequent in Bernese mountain dogs (Moore & Rosin 1986, Padgett et al. 1995, Rossi et al. 2009), Flat-coated retrievers present more commonly with the localised form, particularly the periarticular elbow site (Constantino-Casas et al. 2011). Primary pulmonary HS was first described in 19 Pembroke Welsh corgis in Japan (Kagawa et al. 2015). Recently, a case series of 14 miniature schnauzers described a similar clinical presentation, in which 10 had localised disease and nine of 10 cases were diagnosed with primary pulmonary HS (Lenz et al. 2017). The median survival time of dogs receiving chemotherapy was only
19 days, although they received varied treatment protocols. One of the dogs underwent surgical excision of the primary mass and survived for 1620 days, suggesting a possible role for surgery. This was further explored by Marlowe et al. (2018) describing 37 different breeds from multiple institutions diagnosed with primary pulmonary HS. Dogs undergoing surgery followed by adjuvant lomustine (CCNU)-based chemotherapy appeared to have longer survival in comparison to dogs receiving chemotherapy alone.

The objective of this retrospective, descriptive case series was to report clinical presentation and treatment outcomes in a larger number of miniature schnauzers diagnosed with HS. A secondary goal was to identify prognostic factors influencing progression-free survival (PFS) and overall survival time (OST).

**MATERIALS AND METHODS**

Medical records of miniature schnauzers diagnosed with HS between 2008 and 2019 at two referral centres in the UK were retrospectively reviewed. Information collected from the medical records included signalment, weight, date of diagnosis and treatment initiation, clinical signs at diagnosis including respiratory signs, physical examination findings, laboratory test results [including complete blood count (CBC), serum biochemistry, urinalysis, coagulation tests], method of diagnosis, imaging findings, sites affected, treatment type, response to treatment, date of first progression, rescue treatment and date of death.

Cases with cytological or histopathological diagnosis of HS were included. Fine-needle biopsy smears were stained with Modified Wright’s stain (Hematek Siemens) or Diff-Quik (Atom Scientific). Archived cytological slides of all aspirated sites were reviewed by a single board-certified clinical pathologist if smears were available; otherwise, information was retrieved from the original cytology reports. Cases for which cytology was inconclusive had to have histopathology to confirm the diagnosis of HS. Available histopathology slides were reviewed by a resident-in-training under supervision of a board-certified anatomic pathologist. If possible, immunohistochemistry with CD18 was performed on archived tissue blocks, if not performed at the time of the initial diagnosis. Radiographs, CT and ultrasound findings, including the follow-up studies when available, were reviewed by a board-certified radiologist.

Response to treatment was assessed by the clinician managing the case and, in most cases, was determined by clinical signs, but follow-up imaging was also examined when available. In cases evaluated by monitoring of clinical signs alone, resolution of all clinical signs from the initial presentation was classified as complete response (CR), improvement but without resolution of clinical signs was classified as partial response (PR) and no improvement in clinical signs was classified as progressive disease (PD). For dogs undergoing follow-up imaging, response was classified using Veterinary Cooperative Oncology Group (VCOG v1.1) RECIST criteria (Nguyen et al. 2015). A minimum response duration of 21 days was required to determine response (CR and PR) and dogs that died or were euthanased before 21 days were considered non-responders.

For dogs with a positive response following any form of local or systemic treatment, outcomes were assessed by PFS and OST. PFS was calculated from the date of treatment initiation to the date of local tumour progression/recurrence, metastasis or death from any cause. OST was calculated from the date of treatment initiation to the date of death from any cause. Dogs that were euthanased at presentation were excluded from this analysis. Follow-up information was obtained by phone calls to referring veterinarians and owners when necessary. The study was granted ethical approval by the Clinical Research Ethical Review Board of the primary study institution (protocol number URN SR2019-0237).

**STATISTICAL ANALYSIS**

Descriptive statistics were evaluated for all data variables. Categorical data (sex, anaemia, thrombocytopenia, hypoaalbuminaemia, systemic and/or respiratory signs at initial presentation, primary site affected, anatomical distribution of lesions, other organs affected, pleural effusion, mediastinal involvement, method of diagnosis, type of treatment received) were presented as numbers and/or percentages. Continuous data (age, weight, PFS and OST) were expressed as median and range. The Kaplan–Meier curve was used to illustrate the OST. The data were described and analysed using SPSS statistics software, version 18.0.

**RESULTS**

**Signalment, clinical signs and bloodwork**

Thirty dogs were included (Table 1). Overall, 16 dogs (53%) had respiratory signs at diagnosis. The most common findings on physical examination included muffled heart and lung sounds (n=8, 27%), tachypnoea (n=7, 23%), increased respiratory effort (n=5, 17%) and increased respiratory sounds on one/both sides of the thorax (n=5, 17%).

**Table 1. Signalment and clinical signs at diagnosis (n=30)**

| Characteristics, median (range) |  |
|---------------------------------|---|
| **Age (year)**                  | 10.5 (3 to 12.3) |
| **Weight (kg)**                 | 9.3 (6.7 to 20) |
| **Sex (n)**                     |  |
| Male                            | 18 |
| Female                          | 12 |
| **Clinical signs (n)**          |  |
| Lethargy                        | 19 |
| Decreased appetite              | 18 |
| Weight loss                     | 4  |
| Vomiting/diarrhoea              | 4  |
| Cough                           | 11 |
| Dyspnoea                        | 6  |
| Tachypnoea                      | 4  |
| Neurological signs (seizure, trembling, paraparesis) | 4 |
| PU/PD                           | 2  |
| Uveitis                         | 1  |

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Laboratory abnormalities at the time of diagnosis (CBC and biochemistry performed in 29 and 25 dogs, respectively) were non-specific and included neutrophilia (n=10, 34%), anaemia (n=8, 28%), thrombocytopenia (n=2, 7%), mononucleosis (n=2, 7%), monocytosis (n=2, 7%), mastocytosis (n=1, 4%), elevation of creatine kinase activity (n=6, 24%), elevation of alanine aminotransferase activity (n=4, 16%), elevation of alkaline phosphatase activity (n=4, 16%) and free hypercalcemia (n=1, 4%).

**Imaging findings and staging**

All but one dog underwent some form of imaging. Twenty-nine of 30 dogs underwent thoracic imaging including CT (n=20, 69%), radiographs (n=7, 24%) or ultrasound (n=2, 7%). Twenty-five dogs (83%) had abdominal imaging including CT (n=17, 68%) and ultrasound (n=8, 32%). Twenty-four of 29 (83%) dogs undergoing thoracic imaging had lung and/or mediastinal involvement. The anatomic distribution of thoracic lesions was recorded for dogs undergoing CT imaging. For the remaining dogs in which another imaging modality was performed, only limited information was extracted from the reports (Table 2). On CT, all lesions appeared as soft tissue-attenuating masses (19/20, 90%). In one dog undergoing thoracic imaging no lung or mediastinal lesions were noted.

As part of staging, 11 dogs (37%) had sampling of the spleen (10 for cytological, and one for histopathological examination), which confirmed splenic involvement in four of these 11 dogs (36%). Twelve dogs (40%) underwent sampling of the liver (11 for cytology and one for biopsies during *post mortem* examination) which confirmed HS involvement in three of these 12 dogs (25%). Bone marrow involvement was suspected in one dog with peripheral cytopenias, but was not confirmed. Based on physical examination and imaging findings, 21 dogs (70%) had a suspicion of extra-thoracic organ involvement (summarised in Table 3).

**Cytological and histopathological review**

Twenty dogs (67%) were diagnosed with HS based on cytology findings alone, and three (10%) exclusively by histopathology (without prior cytology); seven (23%) dogs had both cytological and histopathological examination to reach final diagnosis.

Cytological review of the archived slides was performed in 17 cases, 15 of which were consistent with HS. One case was diagnosed as anaplastic malignancy and one as mixed inflammation, with HS not excluded. In both cases, the diagnosis of HS was subsequently confirmed on histopathology. Cytologically, smears diagnostic for HS contained variable numbers of neoplastic round to occasionally more fusiform cells, with oval to reniform nuclei, finely stippled to granular chromatin, prominent nucleoli, and variable amounts of pale basophilic cytoplasm, often containing clear vacuoles (see Figs 1 and 2). Pleomorphism was typically marked, including moderate to marked anisocytosis and anisokaryosis, macrocytosis and karyomegaly, frequent bi- and multinucleation, often with intracellular anisokaryosis and occasional satellite nuclei; occasionally, nuclei of multinucleated giant cells were arranged peripherally. Nucleoli were of variable number, shape and size, including macronucleoli. Mitotic figures were observed in most cases, occasionally in high numbers, and often with aberrant forms. Erythrophagia was observed in 13 cases but was mainly rare, and phagocytosis of leukocytes and cellular debris was found in five cases each. Rare cannibalism was noted in one case. Six aspirates had evidence of necrosis, and inflammation was recorded in 10 cases, including neutrophilic...
inflammation in nine, eosinophilic inflammation in four, lymphocytic inflammation in two.

Histopathological review was available in eight cases. It revealed a pleomorphic and densely cellular malignant round cell tumour. Neoplastic cells were generally arranged in patternless sheets and ranged from plump fusiform to polygonal with often abundant cytoplasm and multiple nuclei, including multinucleated tumour giant cells in most cases. Mitotic figures were frequently observed, including bizarre forms (Fig. 3A, B). Tumours from five dogs labelled strongly and specifically (membranous) for CD18 by immunohistochemistry (Fig. 4A, B). In another two cases, between 10 and 40% of neoplastic cells exhibited specific labelling for CD18 and were morphologically consistent with HS. In a single case the morphology alone was sufficient to make the diagnosis of HS.

**Treatment outcome**

Outcome of all dogs included in the study is summarised in Table 4. Two dogs (7%) received corticosteroids before diagnosis. Eight dogs (27%) were euthanased at the time of diagnosis and another three (10%) were euthanased within 3 days of diagnosis without any treatment. Three dogs (10%) underwent surgery: one enucleation for presumed primary ocular HS, one splenectomy for a primary splenic HS and one right caudal lung lobectomy along with tracheobronchial lymph node excision. The latter case received adjuvant lomustine following surgical excision. Thirteen dogs (43%) received treatment with lomustine as a sole therapy and one additional dog received it following surgery. Three dogs (10%) received palliative treatment with supportive medication including prednisolone and/or analgesia only. For dogs receiving lomustine, the median dose was 59 mg/m² (range: 48.7 to 73).

Of the 13 dogs that received lomustine for gross disease, RECIST response could be evaluated in six dogs; five had PR and one had PD. Clinical improvement was documented in 11 of 13 dogs (85%). Following progression of HS in 11 cases, seven dogs received rescue chemotherapy with a variety of protocols including doxorubicin, epirubicin, vinorelbine, toceranib, chlorambucil and masitinib. Information in the medical record was not detailed enough to classify the responses in all cases.

Eleven of 14 dogs (79%) receiving lomustine had CBC performed after the first dose, where VCOG grade 1, 2, 3 and 4 neutropenia was documented in two (18%), zero (0%), three (27%) and two (18%), respectively. Six dogs (43%) developed alanine aminotransferase activity elevation VCOG grade 2 in three (21%) and grade 3 in three (21%) dogs.

The median OST for all dogs that were not euthanased within the first few days from diagnosis was 117 days (range 10 to 790) (Fig. 5). The median PFS for dogs receiving lomustine in gross disease settings was 117 days (range 22 to 182) and the median OST was 130 days (range 39 to 790. Two dogs that underwent surgery alone survived 45 and 157 days, respectively. Three dogs...
that received palliative treatment only had survived 10, 43 and 89 days, respectively. One dog that underwent lung lobectomy followed by lomustine had PFS and OST of 463 and 501 days, respectively. Due to low number of cases in each group and selective application of different therapies, a meaningful statistical comparison between the treatment groups could not be performed.

All dogs were dead at the end of the study period. All but three dogs died or were euthanased due to HS. One dog suffered from severe tracheal collapse concurrently and was euthanased due to severe respiratory distress while its tumour appeared stable. One dog developed progressive, cumulative thrombocytopenia (PLT <20×10⁹/L), most likely due to chronic chlorambucil administration and was euthanased due to haemorrhagic diathesis. No bone marrow biopsy was performed. One dog developed seizures and, while CT of the brain did not find any mass effect, occult brain metastases were considered a possibility.

## DISCUSSION

We found that the vast majority of miniature schnauzers with HS presented with intrathoracic disease, which is similar to findings of Lenz and others (2017). This unique anatomical localisation of HS has been previously described in the Pembroke Welsh corgi (Kagawa et al. 2015). Localised HS has been shown to have good outcomes with local treatment and adjuvant chemotherapy (Skorupski et al. 2009) with a median survival time of 568 days. However, even with surgical excision, the recently reported survival for primary pulmonary HS (Marlowe et al. 2018) was worse (374 days). In our study, similar to many other studies (Kagawa et al. 2015, Lenz et al. 2017), the described disease course appeared aggressive and reported survival times were short. This is likely influenced by the lack of feasibility of local treatment. Benefit of surgery in pulmonary HS has been suggested by Marlowe et al. (2018) but, in our study, even when localised to the thorax, the disease appeared advanced, often with multiple pulmonary lesions and/or local lymph node involvement. This precluded surgical treatment in most of the cases, similarly to other reports (Marlowe et al. 2018) in which dogs with metastases were less likely to undergo surgery. Nevertheless, one of our cases underwent lung lobectomy and survived >500 days.

More than half of the dogs presented with respiratory signs. Previous studies have found that pulmonary HS affected the right middle lung lobe more commonly than other types of tumours (Tsai et al. 2012, Barrett et al. 2014) but other locations are frequently affected too (Marlowe et al. 2018). In our study, intrapulmonary lesions were widely distributed with one third of the cases having all lung lobes affected. Similar to previous reports, pleural effusion was not a common finding in our study, documented in 14% of previous cases (Shaiken et al. 1991, Schmidt et al. 1993, Tsai et al. 2012). Similar to other reports of HS (Tsai et al. 2012, Marlowe et al. 2018), we commonly noted intrathoracic lymphadenopathy (72%). In most of the cases, as the disease appeared advanced, we did not sample lymph nodes to confirm metastatic disease because it would not have changed the treatment.

Cytological and histopathological examination showed that similar to other reports (Brown et al. 1994, Kagawa et al. 2015, Erich et al. 2018) histiocytic cells typically appear highly pleomorphic and can be accompanied by various inflammatory cells. Most of the dogs in our study experienced positive responses to lomustine. In five of six dogs undergoing follow-up imaging, PRs were documented, even in advanced cases, and 11 of 13 dogs clinically improved. Our response rates are considerably higher than previously described in HS (Skorupski et al. 2007, Rasnick et al. 2010, Cannon et al. 2015), which supports the use of lomustine in gross disease settings even in advanced disease. However, in our study, these responses were short-lived. Among dogs receiving lomustine, five (36%) experienced VCOG grade 3 and 4 neutropenia. Due to the small size of miniature schnauzers, compounded formulations of lomustine were prescribed in all of
| Case | Sex | Age at diagnosis (years) | Primary site | Method of diagnosis | Mediastinum involvement or enlargement | Pleural effusion | Other organ involvement | Treatment | Response type (CR, PR, SD, PD) | Progression-free survival (days) | Rescue protocol used | Total # of CCNU | Overall survival (days) |
|------|-----|------------------------|--------------|---------------------|--------------------------------------|----------------|------------------------|-----------|-----------------------------|-------------------------------|------------------------|----------------|------------------------|
| 1    | MN  | 12.1                   | Lung         | C                   | Y                                    | Y              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 117                         | N                      | 6                      | 117                    |
| 2    | MN  | 7.11                   | Mediastinum  | C and H             | Y                                    | N              | Liver, abdominal lymph nodes, both kidneys | CCNU and prednisolone Palliative | PR (clinical) | 137                         | N                      | 3                      | 137                    |
| 3    | MN  | 10.5                   | Lung         | C, H and CD18+      | Y                                    | N              | Liver                  | CCNU and prednisolone Palliative | PR (clinical) | 137                         | N                      | 3                      | 137                    |
| 4    | FS  | 7                      | Lung         | C                   | Y                                    | N              | Abdominal lymph nodes | None                  | None                       | None                         | None                   | None                   | None                   |
| 5    | MN  | 7.11                   | Mediastinum  | C, H and CD18+      | Y                                    | Y              | Abdominal lymph nodes | None                  | None                       | None                         | None                   | None                   | None                   |
| 6    | M   | 11.1                   | Mediastinum  | C                   | Y                                    | Y              | Spleen                | CCNU and prednisolone Palliative | PR (CT)               | 90                          | Doxorubicin           | 5                      | 191                    |
| 7    | MN  | 7                      | Brain        | H and CD18+         | N                                    | N              | Brain                 | CCNU and prednisolone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 8    | FS  | 6.7                    | Eye          | H and CD18+         | Unknown                             | Unknown       | N                      | Enucleation alone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 9    | MN  | 10.1                   | Mesenteric lymph node | C        | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 10   | M   | 12.3                   | Mesenteric lymph node | C        | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 11   | FS  | 11.1                   | Lung         | C, H and CD18+      | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 12   | MN  | 6.5                    | Lung         | C, H and CD18+      | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 13   | MN  | 9.8                    | Lung         | C                   | Y                                    | N              | Abdominal lymph node | CCNU and prednisolone Palliative | PR (CT)               | 90                          | N                      | 3                      | 191                    |
| 14   | M   | 10.5                   | Mediastinum  | C                   | Y                                    | N              | Jejunal mass          | CCNU and prednisolone Palliative | PR (CT)               | 90                          | Toceranib             | 7                      | 191                    |
| 15   | FS  | 6.7                    | Lung         | C                   | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 90                          | Toceranib             | 7                      | 191                    |
| 16   | MN  | 9.2                    | Lung         | C, H and CD18+      | N                                    | N              | Left kidney, spinal cord | None                  | None                       | None                         | None                   | None                   | None                   |
| 17   | MN  | 6.3                    | Lung         | C                   | Y                                    | Y              | Abdominal lymph node | None                  | None                       | None                         | None                   | None                   | None                   |
| 18   | FS  | 13.1                   | Lung         | C                   | Y                                    | N              | N                      | None                  | None                       | None                         | None                   | None                   | None                   |
| 19   | MN  | 7.5                    | Prescapular lymph node | C        | Y                                    | N              | N                      | None                  | None                       | None                         | None                   | None                   | None                   |
| 20   | FS  | 7.11                   | Lung         | C                   | Y                                    | N              | Spinal cord            | None                  | None                       | None                         | None                   | None                   | None                   |
| 21   | FS  | 8                      | Lung         | C                   | N                                    | N              | Liver, multiple abdominal lymph nodes, other lung lobes | CCNU and prednisolone Palliative | PR (CT)               | 85                          | N                      | 4                      | 125                    |
| 22   | FS  | 8                      | Lung         | C                   | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 85                          | N                      | 4                      | 125                    |
| 23   | FS  | 5                      | Mesenteric lymph node | C        | C                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 85                          | N                      | 4                      | 125                    |
| 24   | MN  | 8                      | Lung/mediastinum | Cytology            | Y                                    | N              | N                      | CCNU and prednisolone Palliative | PR (CT)               | 85                          | N                      | 4                      | 125                    |
| 25   | FS  | 9                      | Spleen       | C, H and CD18+      | Y                                    | N              | Spleen                | Splenectomy alone | None                       | None                         | None                   | None                   | None                   |
| 26   | MN  | 11                     | Mediastinum  | C                   | Y                                    | N              | N                      | None                  | None                       | None                         | None                   | None                   | None                   |
Histiocytic sarcoma in miniature schnauzers

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Our study has multiple limitations. For instance, due to the retrospective nature of this work, dogs neither underwent standard staging procedures nor follow-up evaluations or necropsy, therefore some observations were incomplete. As such, 29 of 30 dogs underwent thoracic imaging and 24 of 30 dogs underwent abdominal imaging. Therefore, if abdominal metastases or important intercurrent disease were overlooked then these could impact on survival making some conclusions unreliable. This, alongside the small numbers of dogs in different treatment groups, precluded meaningful analysis of factors influencing PFS and OST. However, we hope that our findings will pave the way for larger prospective studies examining the clinical progression and response to treatment of HS in this breed of dog. We were not able to retrieve all the cytology or biopsy slides for a standardised review of all cases, and furthermore 20 of the 30 dogs lacked histopathological confirmation of HS. Most cases displayed a characteristic cytological picture, enabling a high degree of confidence in the diagnosis but, in some instances, other sarcomas or highly anaplastic carcinomas could not be ruled out with certainty. However, based on the clinical presentation and response to treatment with lomustine, we believe these differential diagnoses were unlikely.

This study describes the largest population of miniature schnauzers with HS, with clinical presentation supporting previous reports. Although responses to treatment were common, they were usually short-lived due to the aggressive nature of the disease. HS should be considered as a differential diagnosis in miniature schnauzers with pulmonary masses.

Conflict of interest
The authors do not have any conflicts of interest to declare.

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FIG 5. Overall survival time of all dogs
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