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Paraneoplastic hypertrophic osteopathy in 30 dogs

S. S. Withers¹, E. G. Johnson², W. T. N. Culp², C. O. Rodriguez Jr², K. A. Skorupski², and R. B. Rebhun²

¹William R. Pritchard Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California-Davis, Davis, CA, USA

²Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California-Davis, Davis, CA, USA

Abstract

Paraneoplastic hypertrophic osteopathy (pHO) is known to occur in both canine and human cancer patients. While the pathology of pHO is well-described in the dog, very little information exists regarding the true clinical presentation of dogs affected with pHO. The primary objective of this study was to provide a more comprehensive clinical picture of pHO. To this end, we retrospectively identified 30 dogs and recorded data regarding presenting complaints and physical examination (PE) findings on the date of pHO diagnosis. As a secondary objective, any blood test results were also collected from the computerized records. The most common clinical signs included leg swelling, ocular discharge and/or episcleral injection, lameness, and lethargy. The most common haematological and serum biochemical abnormalities included anaemia, neutrophilia and elevated alkaline phosphatase. In addition to presenting a more detailed clinical description of pHO in the dog, these data support the previously described haematological, serum biochemical and PE abnormalities published in individual case reports.

Keywords

comparative oncology; imaging; metastasis; pathology; small animal

Introduction

Hypertrophic osteopathy (HO) is an intriguing syndrome characterized by a painful periosteal reaction and associated soft tissue swelling of the limbs.¹ In the dog, the pathological changes tend to be bilaterally symmetrical and involve all four distal limbs.¹ A separate underlying disease process is the instigating cause, despite the clinical signs of HO frequently becoming apparent prior to those of the primary pathology.² In dogs, HO is most commonly diagnosed as a paraneoplastic syndrome with primary or metastatic pulmonary neoplasia being the most common cause.² Extrapulmonary neoplastic causes have been reported and included tumours of the bladder (undifferentiated sarcoma, botryoid rhabdomyosarcoma) or kidney [transitional cell carcinoma (TCC)].^{2–5} Other reports

describe HO secondary to infectious/inflammatory lung disease, *Dirofilaria immitis* infection, *Spirocerca lupi* oesophageal granuloma, bacterial endocarditis, right to left shunting with a patent ductus arteriosus, oesophageal foreign body or congenital megaesophagus.^{2,6–14}

HO is also well described in people and despite this, the pathogenesis remains elusive.^{15,16} Digital clubbing is a clinical manifestation seen in people but not dogs and is considered to be an earlier stage of the same syndrome as hypertrophic osteoarthropathy, which is the more readily used term in people.¹⁷ The classic pathophysiological changes in HO are increased peripheral blood flow, proliferation of vascular connective tissue and ultimately bone spicule formation.^{1,18} Most recently, it has been proposed that the release of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) from platelets and abnormal platelet circulation may be involved in HO initiation and progression.^{16–18} Other proposed mechanisms include a neural reflex, increased circulating vasodilators or increased growth hormones due to decreased inactivation by the lungs or tissue hypoxia.^{17–20}

A single retrospective description reporting on HO in 60 dogs was published in 1971.² While this case series provides an excellent description of the pathology associated with HO in dogs, very little information is presented regarding the detailed presentation, physical examination (PE) findings or haematological abnormalities associated with HO.² Multiple case reports have more recently described individual cases of HO including detailed PE and blood test findings, however, most of these case reports describe HO associated with uncommon malignancies or infectious/inflammatory diseases.^{4,6–14,21–24} Case report descriptions of HO are often confounded by the presence of the underlying inflammatory disease, making conclusions about their association with a specific process impossible. Therefore, we set out to perform a detailed and thorough investigation of the presenting PE findings, and where available, complete blood count (CBC) and/or serum biochemistry results and thoracic radiographical interpretations in dogs with paraneoplastic HO (pHO). By excluding inflammatory and other non-neoplastic causative processes, the findings can more readily be attributed to the primary neoplasia or pHO. This detailed evaluation of the clinicopathological features of pHO in 30 dogs provides a more complete description of this syndrome and may serve as the basis for further study.

Materials and methods

Dogs with a clinical diagnosis of HO were identified with a search of the electronic medical records at the Veterinary Medical Teaching Hospital of the University of California, Davis. Dogs were included in the study if they had (1) radiographical or histopathological confirmation of HO, (2) a clinical diagnosis of pHO and (3) a recorded PE at the time of pHO presentation. The radiographical diagnosis of HO was based on the appearance of symmetric periosteal new bone proliferation along the long bones of the appendicular skeleton.²⁵

Data were retrospectively collected and recorded from the patient medical records that met the specific inclusion criteria. Historical and presenting complaints by the owners, duration

of clinical signs and PE findings at the time of initial presentation were extracted from the records. Where available, the results of CBC and serum biochemistry panels performed at the time of pHO diagnosis were also reviewed. Histopathological and cytological diagnoses, along with post-mortem findings, were reviewed and correlated with historical data to determine tumour type and differentiate between primary or metastatic disease. Thoracic radiographs performed within 7 days of the diagnosis of HO and limb radiographs were reviewed by a board certified radiologist. They were evaluated for the presence of singular or multiple pulmonary masses or nodules. Pulmonary masses were defined as well circumscribed soft tissue structures within the pulmonary parenchyma measuring greater than 2 cm and nodules were defined as well circumscribed soft tissue structures within the pulmonary parenchyma measuring less than 2 cm. The location and size of the masses in the pulmonary parenchyma was recorded.

Results

Thirty-nine dogs were identified from a search of the computerized medical record database between the years 2000 and 2012 as having a clinical diagnosis of HO. Of these, six dogs were not confirmed to have HO via limb radiographs or post mortem examination, and three dogs were determined to have inflammatory lung disease. The three inflammatory aetiologies consisted of two foxtails and one bacterial endocarditis. These nine dogs were excluded, leaving 30 dogs for inclusion in the study.

The age of the dogs ranged from 3 to 15 years, with a median of 9 years. Seven dogs were mixed breeds. The most common breed identified was the Labrador retriever (four dogs), followed by the Rottweiler (three dogs) and the Doberman pinscher (two dogs). Fifteen dogs were spayed females, 13 were castrated males and there was one each of an intact male and female. Weights ranged from 5.8 to 52.8 kg, with a median of 31.1 kg. At presentation, 7 dogs were receiving a non-steroidal anti-inflammatory drug (NSAID), 2 dogs were receiving prednisone and 13 dogs had undergone some form of chemotherapy in the past.

Clinical signs of pHO were observed by the owner for between 1 day and 6 months before diagnosis, with 21 of the 30 dogs having onset of signs within 3 weeks prior to pHO diagnosis. Three dogs had pHO signs reported for greater than 3 weeks (1 month, 5 weeks and 6 months), in five dogs it was unclear if any clinical signs had been detected by the owners and in one dog the duration of clinical signs was not recorded. Of the five dogs without a record of historical clinical signs, two dogs had multiple bone metastases that may have confounded the distinction of pHO signs and another one dog had a urinary tract obstruction. The most common presenting clinical sign was swelling of the limbs seen in 26 of the 30 dogs. Most dogs (15/26) had swelling of all remaining limbs, whereas five dogs had only thoracic limb involvement and two dogs had only pelvic limb involvement. The remaining four dogs had swelling localized to a single leg (two right thoracic limbs, one left thoracic limb and one right pelvic limb). In all cases, the swelling was either distal or encompassing the whole leg. In two of the dogs without limb swelling, severe signs secondary to the instigating neoplastic process were present including TCC metastasis to the spine and long bones resulting in severe tetraparesis and recumbency, and urethral obstruction because of prostatic carcinoma. It is therefore possible that in these patients,

limb swelling was overshadowed by more emergent clinical findings. Conversely, three patients reported as having limb swelling also had evidence of metastasis to the musculoskeletal system, which likely contributed to this finding. The remaining clinical signs recorded were lameness or difficulty ambulating (23/30), ocular discharge or episcleral injection (23/30), lethargy (22/30), decreased appetite (15/30), pyrexia (11/30), pain on palpation of extremities (11/30), coughing (9/30), heat on palpation of limbs (6/30) and an inability to rise or ambulate (3/30).

Nine dogs displayed coughing at the time of presentation, which was seen concurrently with other clinical signs (i.e. limb swelling, lameness, lethargy) in all dogs. The remaining 21 dogs were not reported to be coughing. In three dogs in which no respiratory signs were observed at the time of pHO diagnosis, clinical signs were referable to the primary disease process, rather than pHO. This included two dogs exhibiting a difficulty or inability to ambulate due to skeletal metastasis from TCC and urinary obstruction in one dog with TCC.

Of the 23 dogs that displayed ocular signs on presentation, signs consisted of bilateral serous to mucopurulent discharge (21/23) and/or mild to severe episcleral injection (15/23). In most of these dogs (16/23), no ocular signs were reported or documented during PE before pHO diagnosis. In five dogs, ocular signs were either reported to be a chronic, intermittent problem by the owner or were recorded in the history prior to signs of pHO arising. Insufficient records were available in two dogs to report on this. In two dogs with Schirmer tear test measurements and ocular signs coinciding with pHO signs, keratoconjunctivitis sicca (KCS) was suspected and medication recommended. One of these dogs had a Schirmer tear test result of 13mm bilaterally taken at the time clinical signs of pHO first arose. The other dog had measurements of 13 and 15mm in the right and left eyes, respectively but due to the persistent clinical signs was treated for KCS despite the marginal results.

CBC values were available on the day of pHO diagnosis for 20 dogs. The most common abnormality was anaemia (13/20, reference range 40–55%) of which most were non-regenerative as determined by a normal reticulocyte count (9/13, reference range 7000–65 000 μL). In the 13 anaemic dogs, the range in haematocrit was 26.3–38.5%, with a median of 32.7%. In all 20 dogs with an evaluable haematocrit, the range was 26.3–49.9%, and the median was 35.1%. In 7 of the 13 dogs, the anaemia was characterized as a microcytic, hypochromic anaemia, with 4 being non-regenerative and 3 being regenerative. In another 3 of the 13 dogs, the anaemia was determined to be microcytic, normochromic and non-regenerative. Two dogs had a normocytic, normochromic anaemia of which one was regenerative and the other non-regenerative. The remaining dog had a hypochromic, non-regenerative anaemia. A neutrophilia was observed in 11 of the 20 dogs with a range of 11 322–34 813 μL and a median of 14 181 μL (reference range 3000–10 500 μL), 2 of which also demonstrated a left shift. In all 20 dogs with an evaluable neutrophil count the range was 3540–34 913 μL with a median of 11 526 μL . Two additional dogs displayed circulating neutrophilic bands with no neutrophilia. Thrombocytosis was detected in 5 of the 20 dogs, whereas thrombocytopenia was detected in 1 dog with a concurrently increased mean platelet volume (MPV). This dog was diagnosed with disseminated intravascular coagulation (DIC) in addition to a primary pulmonary carcinoma, with elevations of clotting times, decreased fibrinogen and detection of D-dimers.

Eleven of the 18 dogs that had alkaline phosphatase (ALKP) measured on the date of pHO diagnosis had elevation of this enzyme above the upper limit of normal with a range of 152–437 IU L⁻¹ and a median of 237 IU L⁻¹. Two of these 11 dogs had a history of receiving corticosteroids within the preceding 3 weeks. Six of these 11 dogs had osteosarcoma but only 2 had associated lytic lesions at the time of pHO diagnosis. An additional 2 of the 11 dogs with elevated ALKP had bony lesions due to metastatic TCC. One of the dogs with osteosarcoma was also receiving prednisone, leaving only two dogs with ALKP elevations without any of the possibly contributing factors mentioned. Elevation of serum globulin was observed in 3 of the 18 dogs (with values of 3.2, 3.8 and 4.9 g dL⁻¹) and hypoalbuminaemia was detected in 11 of the 19 dogs (with a range of 2.0–2.8 g dL⁻¹ and a median of 2.3 g dL⁻¹); these abnormalities were seen concurrently in one of these dogs.

All 30 dogs in this study had a clinical diagnosis of neoplastic pulmonary nodules. Seventeen dogs had fine-needle aspirate or biopsy confirmation of neoplastic nodules within the lungs. Three of the 17 dogs were determined to have primary pulmonary adenocarcinomas. The remaining 14 out of the 17 dogs with cytologically or histologically confirmed pulmonary neoplasia had clinical diagnoses consistent with metastatic disease. Nine of these 14 dogs had metastatic osteosarcoma (6 appendicular, 1 subcutaneous, 1 rib and 1 in which the primary tumour was not found on necropsy), 2 had metastatic TCC, 2 had sarcomas (1 leiomyosarcoma and 1 fibrosarcoma) and 1 had neoplasia of uncertain type (with a history of mammary adenocarcinoma).

The remaining 13 of 30 dogs had radiographical pulmonary lesions consistent with neoplastic disease but no cytology or histopathology was performed. Of these, 11 had a history of a prior or concurrent malignancy. The most common was appendicular osteosarcoma in six dogs, whose primary tumours had been identified between 1 and 11 months prior to the development of HO. Other malignancies included one each of bladder TCC, prostatic carcinoma, renal carcinoma, renal adenocarcinoma with osteosarcomatous differentiation, and appendicular chondrosarcoma. Two dogs did not have a history of a malignancy and were considered most likely to have a primary pulmonary neoplasia based on the radiographical findings of a single lung mass with an absence of hilar lymphadenopathy. Neither of these two dogs had blood testing performed on the date of pHO diagnosis and so they do not contribute to the blood test findings reported.

Twenty-five dogs had thoracic radiographs performed within 7 days of the pHO diagnosis, and these were reviewed by a radiologist. The remaining five dogs had thoracic radiographs indicating pulmonary masses/nodules performed many weeks prior to the diagnosis of pHO, or these were performed at the time of pHO diagnosis but were unavailable for review. The most common radiographical findings in dogs with pHO were multiple, diffuse, variably sized, well-circumscribed pulmonary nodules and masses. Only three dogs had a solitary pulmonary mass. In one dog no pulmonary metastases were evident on radiographs at the time of diagnosis, but gross nodules were evident on necropsy the day after initial presentation. There did not appear to be consistent radiographical findings regarding location, size, or number of pulmonary nodules or masses in dogs with pHO.

Necropsy was performed on nine dogs. In addition to the pulmonary neoplasia and pHO previously described, other significant findings included three dogs with metastases to axial and/or appendicular bone, another two dogs had metastases to muscle and one dog had concurrent salivary gland necrosis and amyloidosis of the liver, spleen and adrenal glands.

Discussion

This study aimed to provide a more thorough and complete description of the clinical presentation of pHO in dogs. Several clinical abnormalities appeared to be shared by many of the dogs in this study, including limb swelling, ocular signs, lameness and lethargy. In addition, haematological and serum biochemical abnormalities such as anaemia, neutrophilia and elevated ALKP were relatively common.

The epidemiologic features of the patients included in this study are consistent with previous reports in that the wide range of ages, weights and breeds present reflects the heterogeneous group of tumour types that can initiate HO.² The median age of 9 years is expected due to the propensity for cancer to develop in dogs in the latter stages of their life. The median weight of 31.1 kg is thought to be secondary to the relatively high number of dogs with appendicular osteosarcoma (12/30), which tends to predominantly occur in large and giant breed dogs.

Historically, clinical signs associated with HO in dogs are predominated by lameness, reluctance to ambulate and swelling of the distal limb.^{1,2,4,5,9–14,22,23,26–30} The swelling may or may not be associated with pain and heat. Respiratory signs or other signs of the underlying disease process are occasionally concurrently apparent.^{1,2,5,9,11–14,23,26,29} Ocular signs consisting of injected ocular mucous membranes and bilateral mucopurulent ocular discharge have infrequently been reported in dogs diagnosed with HO in the past.^{13,14} In addition, haematological and serum biochemical alterations such as anaemia, neutrophilic leukocytosis with or without a left shift, thrombocytosis, thrombocytopenia, elevated ALKP, hypoalbuminaemia and hyperglobulinaemia are frequently observed.^{4,9,10,12,14,23,27,29}

Previous reports on HO have identified distal limb swelling as a unifying clinical feature in dogs.^{1,2} In our report, 4 of the 30 dogs were not recorded as displaying this trait, however, this may have been overlooked due to the presence of far more serious clinical signs in two dogs. Nevertheless, the most common clinical sign observed in this study was also limb swelling and was found even in two dogs that presented with no history of limb problems.

Other observed clinical signs such as lameness and difficulty ambulating, lethargy, decreased appetite, apparent pain on palpation and an inability to rise are likely secondary to the discomfort that has been described by people affected with this syndrome.³¹ Imaging studies have detected increased blood flow to clubbed fingers in people along with dilated blood vessels histopathologically.¹⁶ This likely explains the common finding of heat associated with the limb swellings in this study and others.^{1,2,4,12,16,23,28} Pyrexia, reported in 11 dogs in this study, is also a common finding in both people and dogs and probably contributes to the severity of the other clinical signs observed.^{4,10,13,14,28,29,32} The mechanism for

paraneoplastic fever has been postulated to be due to excess production of cytokines such as IL-1, IL-6, TNF-alpha and interferons, along with febrile-promoting prostaglandins.³³ It is also possible that the fever observed in these dogs may be directly associated with pHO, stress, excitement or pain. Therefore, investigation of cytokine levels in dogs presenting with pHO is indicated to attempt to elucidate the pathogenesis of fever in some of these dogs.

Interestingly, the majority of the dogs (23/30) described in this series were reported to have ocular abnormalities on PE and in some cases were included in the presenting complaint. Most of these dogs had no previous ocular problems reported, although it is accepted that the retrospective nature of this study makes it difficult to determine if these signs actually did occur at the onset of pHO. While it is interesting that two dogs were diagnosed with mild KCS, a thorough ocular examination was not performed in the majority of cases and therefore it is impossible to know the pathological process occurring in the remaining cases. Nevertheless, the large proportion of dogs displaying ocular signs was thought to be an interesting finding. Potential, unrelated causes of ocular signs in these dogs are plentiful and include adverse effects to medications and pre-existing ocular disease. We can therefore make no association between pHO and ocular signs. One dog in our cohort with osteosarcoma and extensive metastatic disease to the lungs and other sites, was also diagnosed with salivary gland necrosis at necropsy. The pathogenesis of salivary gland necrosis in dogs remains elusive but has been hypothesized to parallel that of HO.³⁴

In 21 dogs, coughing was not seen at presentation with pHO. The remaining nine dogs displayed coughing in addition to signs correlating either to the primary tumour or to the pHO. This is consistent with a previous report, in which 37 of the 53 dogs showed HO signs prior to respiratory signs and 8 of the 53 dogs had concurrent signs.² However, it is not clear how many dogs had respiratory disease reported on the date of HO diagnosis in this previous case series, making direct comparison of these data difficult. Regardless, it is clear that relatively few dogs will display respiratory signs at the time when pHO signs become apparent.

Non-characterized anaemias have been reported previously in dogs with HO.^{4,14} In this article, the most common abnormal blood test finding in this report was anaemia, most of which were microcytic with or without hypochromasia, and non-regenerative. Microcytic, hypochromic anaemia is typical for iron deficiency anaemia.³⁵ Iron deficiency anaemia secondary to gastrointestinal bleeding may have been precipitated by administration of an NSAID or prednisone at the time of pHO diagnosis in less than half of the dogs affected. However, chronic blood loss is required for evidence of iron deficiency anaemia to arise and the short duration of administration of potentially ulcerative drugs in these few patients seems therefore the unlikely instigating cause.³⁵ It is also possible that anaemia of inflammatory disease may have been involved in individual patients.³⁵ It is likely that the administration of chemotherapy to 5 of the 13 dogs that displayed anaemia, may have played a role as well. Prior CBC values were available in 7 of the 13 dogs with anaemia, at varying time points, and only 2 dogs had a history of anaemia prior to presentation with pHO, which further supports the association of anaemia with this syndrome. Of course the mere progression of neoplastic disease in patients that have developed pHO would also likely be involved in the development of anaemia. Interestingly, cellular iron deficiency has been

found to increase VEGF production and angiogenesis *in vitro*, which are involved in some theories of HO pathogenesis.^{16,36} Therefore, it is possible that iron sequestration in dogs with cancer may result in decreased haemoglobin synthesis, resulting in the finding of anaemia in these dogs.³⁷

Neutrophilia and thrombocytosis are commonly reported in dogs diagnosed with HO.^{4,9,10,14,20,23,29} Consistent with historical case reports, most dogs with blood work available in this study displayed neutrophilia, despite the specific exclusion of patients with primary inflammatory disease. This finding may be due to stress, inflammation surrounding the new bone formation or possibly secondary to the underlying neoplastic process. Thrombocytosis was a less frequent abnormality in our study, and may be secondary to iron deficiency anaemia, or as part of a paraneoplastic process, but most likely was due to inflammation. Only one dog in this series displayed thrombocytopaenia and an elevated MPV and this dog was diagnosed with DIC in addition to a primary pulmonary carcinoma, with elevations of clotting times, decreased fibrinogen and detection of D-dimers. It is reasonable to conclude that this patient's platelet abnormalities were secondary to DIC rather than pHO.

Platelet abnormalities have been reported in humans with HO and are thought to possibly play a role in the syndrome's pathogenesis.³⁸ It has been previously postulated that human patients with hypertrophic osteoarthropathy secondary to conditions that alter the normal pulmonary circulation such as chronic lung inflammation, bronchial tumours or intra-cardiac right to left shunts, may have decreased normal fragmentation of platelets in the lungs, resulting in macroplatelets lodging in the small vessels of the extremities.¹⁶ In our study, few dogs showed significant platelet abnormalities. Therefore, if further investigation into platelet abnormalities in dogs with pHO was to be performed, establishment of standard collection methods and investigation of platelet function and mean MPV would be necessary.

Elevation of serum ALKP is reported in people and dogs with HO and was found in most dogs with values available for review in this study.^{9,27,29,31} This is presumably due to enhanced osteoblast activity as part of the HO progression but may also have been secondary to bone metastases in at least four dogs (three confirmed and one suspected based on radiographs) and prednisone administration in another two dogs in this study. Seven of these 11 dogs with ALKP elevations had osteosarcoma but only 2 of these dogs had bone lesions at the time of pHO diagnosis. In 6 of these 11 dogs, prior chemistry values were available and indicated that 3 of these 6 dogs had prior ALKP elevations and 3 did not.

Hypoalbuminaemia and hyperglobulinaemia are also commonly reported biochemical abnormalities in dogs with HO.^{9,10,23} These nonspecific findings were also detected in many of the dogs described here. The hypoalbuminaemia may be present in these patients secondary to inflammation, undiagnosed renal losses, malabsorption, malnutrition or secondary to elevated globulins. Hyperglobulinaemia is likely the product of inflammation secondary to HO or the primary neoplastic disease.

In this study, all dogs with pHO had neoplastic pulmonary disease. Six dogs had findings consistent with primary pulmonary tumours and the remaining 24 were thought to have

metastatic disease. Similarly, Brodey *et al.*² described 54 of the 55 dogs with pHO as having pulmonary disease with the majority (35/54) being metastatic lesions. The most common tumour type in both this and the Brodey² series was osteosarcoma, likely reflecting the higher prevalence of this tumour type and its propensity for pulmonary metastasis. A major limitation of this study is the lack of cytological or histopathological diagnoses for all dogs. It is thought, however, that the most important information obtained from review of these cases is the clinicopathological manifestation of HO and the radiographical review of the lesions, rather than the specific inciting cancer histologies. However, it is accepted that the tumour itself can contribute to some of the abnormal findings observed, and that some tumour types have a greater propensity to do this than others. Since HO is a secondary disease syndrome in dogs, we are unable to ever observe the effects of this pathology in isolation. The common clinical features of dogs included in this study can therefore never be definitively correlated with pHO itself, but are rather concurrent findings seen in dogs afflicted by this syndrome. By characterizing HO in dogs due to a neoplastic cause, we aimed to merely minimize the contribution of the primary disease to the clinicopathological findings observed.

Information regarding treatment and outcome for the patients described here was not reported as the vast array of different therapies administered and the frequent lack of follow-up made this data difficult to interpret. Several previous reports have described therapeutic outcomes and it is clear from these that resolution of pHO is best achieved by removal of the inciting cause, although resolution may be fleeting if progression of pulmonary metastasis occurs.^{2,4,5,24,27,39} With a better understanding of the pathogenesis of this syndrome, therapeutic options may become apparent for cases in which advanced metastatic disease precludes the option of surgical excision.

In undertaking a retrospective description of the clinical and pathological findings seen in 30 dogs presenting with pHO, we identified several common clinical features that had been previously described in individual case reports. Prospective studies are warranted to attempt to understand the aetiology of these abnormalities seen concurrently with pHO in dogs.

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