CASE REPORT

Journal of Veterinary Internal Medicine ACVIM
Open Access American College of Veterinary Internal Medicine

Congenital dyserythropoiesis and polymyopathy without cardiac disease in male Labrador retriever littermates

Alison Thomas-Hollands[1] | G. Diane Shelton[2] | Ling T. Guo[2] |
Kerry Loughran[1] | Gregory Kaiman[1] | Tabitha A. Hutton[3] | Koranda A. Walsh[4]

[1]Department of Clinical Sciences and Advanced Medicine, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Department of Pathology, University of California San Diego, La Jolla, California, USA

[3]Metropolitan Veterinary Associates, Norristown, Pennsylvania, USA

[4]Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Koranda A. Walsh, Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, 3900 Delancey St, Clinical Lab Room 4101, Philadelphia, PA 19104.
Email: koranda@upenn.edu

Abstract

Background: Two Labrador retriever littermates were identified based on incidentally noted marked microcytosis and inappropriate metarubricytosis. Muscle atrophy was noted and associated with distinctive pathological findings in biopsy samples from 1 dog studied. The disorder represents a rare clinical entity of suspected congenital dyserythropoiesis and polymyopathy. Clinicopathologic changes were similar to a previously reported syndrome of congenital dyserythropoiesis, congenital polymyopathy, and cardiac disease in 3 related English Springer Spaniel (ESS) dogs, but the dogs reported here did not have apparent cardiac disease.

Interventions: Bone marrow aspiration, electromyography, muscle biopsies, and an echocardiogram were performed on dog 1. Results supported dyserythropoiesis and congenital polymyopathy similar to reports in ESS dogs, but did not identify obvious cardiac disease.

Conclusion: The clinicopathologic changes of dyserythropoiesis and polymyopathy provide an easily recognizable phenotype for what appears to be a low morbidity syndrome. Early recognition may decrease unnecessary testing or euthanasia.

KEYWORDS
anemia, dyserythropoiesis, metarubricytosis, microcytosis, muscle atrophy, polymyopathy, regurgitation

1 | INTRODUCTION

Dyserythropoiesis refers to defective development of red blood cells and encompasses pathological alterations in both the morphology and function of erythrocytes.[1] Presenting clinical signs include anemia and suboptimal reticulocyte response.[2] In humans, several congenital dyserythropoietic anemias occur. In dogs, congenital anemias have

been described and more commonly are associated with enzyme deficiencies.[3]

Congenital myopathies in people[4] and dogs[5] are defined as a heterogeneous group of nondystrophic neuromuscular disorders classified based on predominant, usually structural, pathological findings in muscle biopsy samples.[4] Presenting clinical signs in patients with congenital myopathies include weakness, muscle atrophy, dysphagia, and regurgitation. Several examples of congenital myopathies in dogs exist,[6-12] some of which are associated with known genetic mutations.[7,9,11,12] Both X-linked myotubular myopathy (XLMTM)[8,9] and centronuclear myopathy (CNM)[7] have been described in Labrador

retrievers, and mutations have been identified. A consistent feature among centronuclear and myotubular myopathies is the presence of numerous centrally placed nuclei and prominent central staining with the oxidative histochemical reactions of cytochrome C oxidase (COX) and succinic dehydrogenase (SDH).[7-9,11]

A previous study described a condition of congenital dyserythropoiesis, polymyopathy, and cardiac disease in 3 related English Springer Spaniel (ESS) dogs.[13] The dogs had marked inappropriate metarubricytosis with substantial microcytosis along with spherocytes, schistocytes, and codocytes. They also had slowly progressive polymyopathy with temporal muscle atrophy and less pronounced generalized skeletal muscle atrophy, megaesophagus, and cardiac abnormalities including right ventricular enlargement. Pathological changes in muscle biopsy samples in the ESS dogs consisted of many myofibers containing central nuclei, excessive variability in myofiber size, and central linear and mottled inclusions. The underlying cause was not determined, and the condition has not been described since this initial case series.

The purpose of our report is to describe the clinical presentation and diagnostic testing results for 2 related Labrador retrievers with dyserythropoiesis and congenital polymyopathy but without apparent cardiac disease that were phenotypically similar to the previous report in 3 ESS dogs. Early recognition of this unique clinical presentation may allow for a more targeted diagnostic and treatment approach in what appears to be a low morbidity clinical syndrome.

2 | CASE 1: HISTORY AND DIAGNOSTIC TESTING

A client-owned, 5-year-old, 38 kg, male neutered Labrador retriever was presented to the Internal Medicine service at the University of Pennsylvania Veterinary Hospital. The dog had a history of erythrocyte abnormalities discovered incidentally on precastration laboratory testing at 3.5 years of age. The dog also had intermittent pelvic limb weakness, regurgitation, and generalized muscle atrophy, most pronounced over the temporalis muscles. On further review, an in-house CBC performed when the dog was 7 months old identified severe microcytosis (mean cell volume [MCV], 41 fL; reference range [RR], 60-72 fL).

Initial testing, before presentation to the University of Pennsylvania Veterinary Hospital, included multiple diagnostic tests with several abnormalities. A pathologist-reviewed CBC identified substantial microcytosis (MCV, 42 fL; RR, 59-78 fL), marked metarubricytosis (nucleated red blood cell [nRBC], 25/100 white blood cells [WBC]; RR, 0-1/100 WBC) in the absence of regeneration (reticulocytes, $38 \times 10^3/\mu L$; RR, $10\text{-}110 \times 10^3/\mu L$), moderate numbers of codocytes, and rare schistocytes. Abdominal ultrasound examination disclosed severe generalized splenomegaly and a left intra-abdominal testicle. The dog underwent routine splenectomy, liver biopsy, and castration. On histopathology, the liver and testicle had no clinically relevant abnormalities. Splenic histopathology identified hematomas without evidence of neoplasia. All other test results were negative (fecal

flotation, SNAP 4Dx, comprehensive vector-borne disease PCR [Babesia, Bartonella, Anaplasma, Ehrlichia, Rickettsia, Mycoplasma] and serology [Babesia canis + gibsoni, Ehrlichia canis, Rickettsia rickettsii, Bartonella henselae, Bartonella vinsoni, Bartonella koehlerae]) or within normal limits (serum biochemistry panel without creatine kinase [CK] activity, blood lead concentration, thoracic radiographs).

On repeat CBC, the dog had persistent marked metarubricytosis (nRBC, 48/100 WBC; RR, 0-1/100 WBC) and microcytosis with similar morphologic abnormalities. A reticulocyte count was not performed. Additional diagnostic testing including an iron panel (total serum iron concentration, total iron binding capacity), and serum cobalamin and folate concentrations were within normal limits. A baseline serum cortisol concentration was 0.9 μg/dL (RR, 2-6 μg/dL).

At presentation to the University of Pennsylvania Veterinary Hospital, 19 months after initial evaluation, the dog had developed regurgitation, moderate temporal muscle atrophy, and mild generalized muscle atrophy. Overall body condition score was normal. Physical and neurologic examinations were otherwise normal. Diagnostic tests were performed to further investigate the hematologic, gastrointestinal, and neuromuscular abnormalities. Because of the similarities to the previously reported dyserythropoiesis and myopathy in ESS dogs,[13] a cardiac evaluation also was performed.

A CBC with pathologist review identified marked microcytosis (MCV, 49.4 fL; RR, 64-76 fL) and slight hypochromasia (mean corpuscular hemoglobin concentration, 31 g/dL; RR, 33-36 g/dL) with mild anemia (hematocrit, 34.5%; RR, 41-58%) without regeneration (reticulocytes, $89.9 \times 10^3/\mu L$; RR, $11\text{-}92 \times 10^3/\mu L$), marked metarubricytosis (nucleated RBC, 86/100 WBC; RR, 0-1/100 WBC), and poikilocytosis
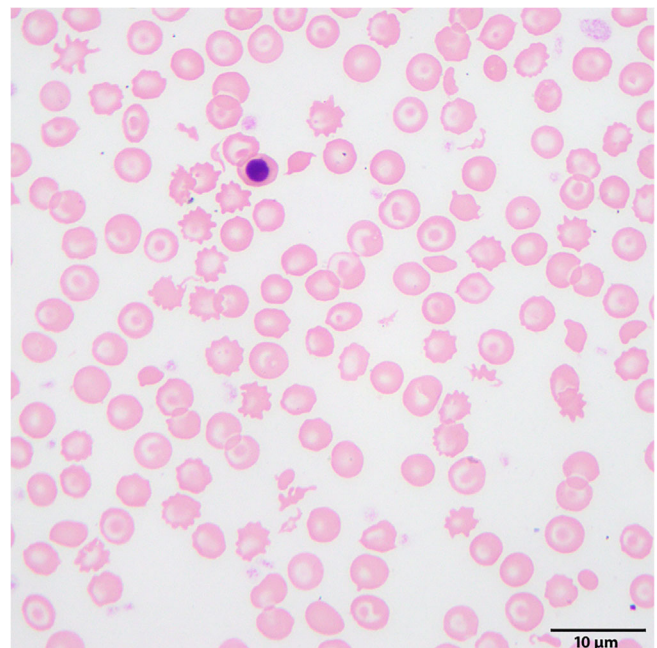
FIGURE 1 Representative blood film image of case 1 displaying a single metarubricyte as well as moderate to marked overall poikilocytosis characterized by schistocytes, codocytes, and acanthocytes. Wright-Giemsa, ×100 objective

characterized by schistocytes, codocytes, acanthocytes (Figure 1), and rare spherocytes. The leukocyte and platelet counts were within RR.

On bone marrow cytologic evaluation, the marrow was cellular, with 90% to 95% particle cellularity and a decreased myeloid-to-erythroid ratio (0.2:1). The erythroid lineage was complete but appeared unbalanced with numerous metarubricytes relative to the degree of polychromasia, and the lineage displayed dysplastic changes characterized by frequent cytoplasmic vacuolation (especially in metarubricytes), multinucleated cells, cytoplasmic bridging, and atypical mitotic figures (Figure 2). There were low numbers of macrophages containing phagocytized debris as well as mature red blood cells and metarubricytes (Figure 2). The myeloid and megakaryocytic lineages were normal. Prussian blue staining indicated abundant iron in macrophages. No neoplastic cells were identified. Bone marrow core histopathologic evaluation was similar to cytologic findings of bone marrow aspirates, with no additional findings.

Thoracic radiographs identified a markedly gas-distended esophagus consistent with megaesophagus but were otherwise normal. An acetylcholine receptor antibody titer (0.05 nmol/L; RR, <0.6 nmol/L) and serum total thyroxine (T4) concentration (1.02 μg/dL; RR, 1-4 μg/dL) were within normal limits. An adrenocorticotropic hormone (ACTH) stimulation test was within normal limits (pre-ACTH serum cortisol concentration, 3.07 μg/dL; RR, 2-6 μg/dL; post-ACTH serum cortisol concentration, 13.0 μg/dL; RR, 6-18 μg/dL). Serum CK activity was normal (145 U/L; RR, 46-467 U/L).

Cardiovascular physical examination identified a grade I/VI left apical systolic murmur. Six-lead ECG showed sinus arrhythmia. The mean electrical axis was 108° (slight right axis deviation). Two-dimensional transthoracic echocardiography was performed. Left ventricle internal dimensions normalized to body weight (Norm-LVDs, Norm-LVDd) were mildly increased in systole (Norm-LVDs, 1.2; RR, <1.14[14]) and diastole (Norm-LVDd, 1.8; RR, <1.73[14]). The echocardiogram was otherwise normal.

Needle electromyography was performed and limited to the left temporalis, supraspinatus, infraspinatus, biceps, triceps, quadriceps, biceps femoris, and gastrocnemius muscles. No abnormal electrical activity was identified in any muscle group. Muscle biopsy samples were collected from the contralateral right biceps, triceps, and frontalis muscles. Biopsy specimens were either unfixed and snap frozen or fixed and paraffin embedded. Cryosections were processed using standard histochemical stains, including hematoxylin and eosin (H&E), modified Gomori trichrome, myofibrillar ATPase reactions at pH 9.8, 4.5, and 4.3, periodic acid-Schiff, oil red O, nonspecific esterase, acid and alkaline phosphatase, nicotinamide adenine dinucleotide dehydrogenase, SDH, and COX.[4]

Similar pathological changes were found in all 3 muscles (Figure 3). Marked variability in myofiber size was present (fiber diameters ranging from 17-88 μm) with numerous atrophic or hypotrophic fibers having round to anguloid shape. The percentage of myofibers containing centrally located nuclei (Figure 3A) as assessed by counting
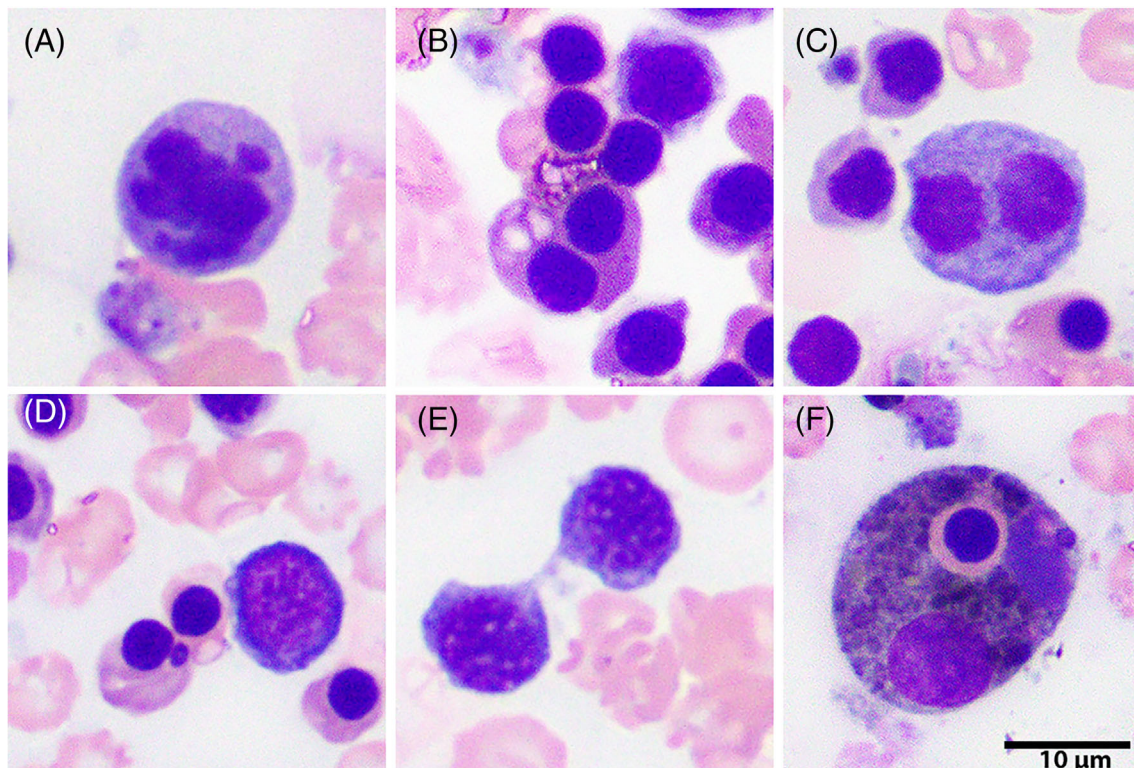
FIGURE 2   Representative cytologic bone marrow images of case 1 illustrating dysplastic changes and erythrophagocytosis. Wright-Giemsa, ×100 objective. A, Atypical mitotic figure; B, cytoplasmic vacuolation of metarubricytes. Note the contrast of vacuolation (left metarubricyte) compared to water artifact (adjacent right metarubricyte), C, binucleated erythroid precursor; D, nuclear blebbing within a metarubricyte; E, cytoplasmic bridging of rubricytes; F, macrophage displaying metarubricyte phagocytosis
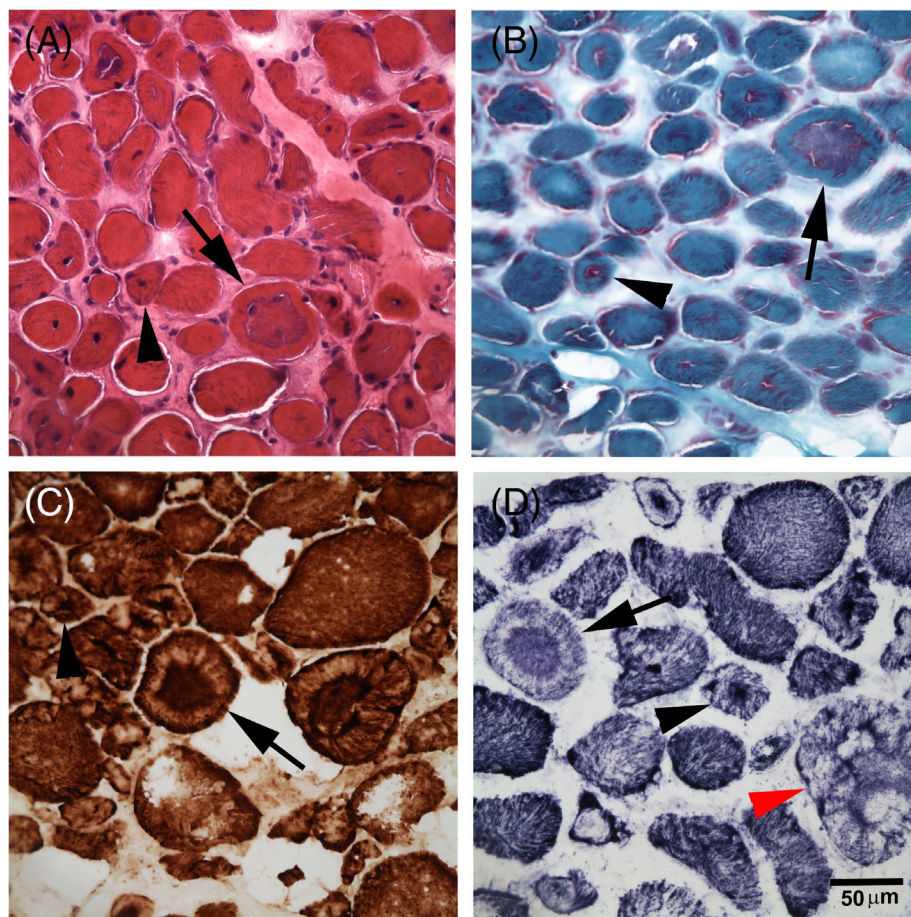
FIGURE 3 Cryosections from the triceps muscle of case 1 stained with hematoxylin and eosin (H&E), A, and modified Gomori trichrome, B, or reacted for cytochrome C oxidase, C, and succinic dehydrogenase, D, activities. Prominent findings are variability in myofiber size, central nuclei (arrow heads), and central accumulations of reactivity that are basophilic with the H&E stain and red with the modified Gomori trichrome stain, and dark brown or dark blue with the cytochrome C oxidase and SDH reactions, respectively (arrows)

the number of centrally located nuclei/100 fibers was approximately 30% in the triceps muscle and 36% in the frontalis muscle (RR, <3% in transverse sections). Additional myofibers contained large areas of central staining that were basophilic on H&E staining (Figure 3A) and red with the modified Gomori trichrome stain (Figure 3B). Additional reactions showed that these areas stained brown with the COX reaction (Figure 3C) and dark blue with the SDH reaction (Figure 3D), indicating abnormal localization of mitochondria. No inflammation, necrosis, fibrosis, organisms, or other specific cytoarchitectural abnormalities were observed. These findings supported a noninflammatory, congenital myopathy with pathological changes consistent with the centronuclear/myotubular myopathy group of neuromuscular diseases. Given the similarities between the pathological changes in XLMTM[9] and CNM[7] reported in the Labrador breed, genotyping was performed for the published mutations. The dog was wild type for both *MTM1* and *PTPLA1* variants.

3 | CASE 2: HISTORY AND DIAGNOSTIC TESTING

A client-owned, 5-year-old, 25.7 kg, male neutered Labrador retriever was presented to the Internal Medicine service at Metropolitan Veterinary Associates for suspected vomiting (later determined to be

regurgitation), weight loss, and muscle atrophy, most notably of the temporalis muscles. This dog was a littermate of dog 1. Review of prior medical records identified persistent microcytosis (MCV, 45 fL; RR, 58-79 fL) and metarubricytosis (nucleated RBC, 12/100 WBC; RR, 0-1/100 WBC) documented on precastration blood work performed at 1 year of age.

Before presentation to Metropolitan Veterinary Associates, a CBC indicated substantial microcytosis (MCV, 38 fL; RR, 61.6-73.5 fL) and inappropriate metarubricytosis (nucleated RBC, 22/100 WBC; RR, 0-1/100 WBC) without regeneration (reticulocytes, $64 \times 10^3/\mu L$; RR, $10\text{-}110 \times 10^3/\mu L$). A serum biochemistry panel was normal including CK activity. Other test results were negative (SNAP 4Dx and fecal flotation). Abdominal ultrasound examination identified pyloric thickening. Referral for upper gastrointestinal endoscopy was recommended. On presentation at Metropolitan Veterinary Associates, the patient exhibited moderate diffuse muscle atrophy with more severe atrophy noted of the muscles of mastication. No neurologic examination abnormalities were noted.

4 | CASE 2 RESULTS

A CBC with pathologist review corroborated microcytosis (MCV, 41 fL; RR, 59-76 fL), metarubricytosis (nucleated RBC, 7/100 WBC;

RR, 0-2/100 WBC), and the presence of acanthocytes, keratocytes, schistocytes, and codocytes. Leukocytosis ($22.1 \times 10^3/\mu L$; RR, 4.9-$17.6 \times 10^3/\mu L$) with neutrophilia ($19.7 \times 10^3/\mu L$; RR, 2.9-$12.7 \times 10^3/\mu L$), a left shift ($221/\mu L$; RR, 0-$170/\mu L$), lymphopenia ($0.884 \times 10^3/\mu L$; RR 1.06-$4.95 \times 10^3/\mu L$), and monocytosis (1.326; RR 0.13-$1.15 \times 10^3/\mu L$) were present. A serum biochemistry panel was unremarkable. An ACTH stimulation test was within normal limits (pre-ACTH serum cortisol concentration, 3.6 μg/dL; RR, 2-6 μg/dL, post-ACTH serum cortisol concentration, 19.8 μg/dL; RR, 6-18 μg/dL). Additional tests were unremarkable (serum cobalamin concentration, 902 ng/L; RR, 251-908 ng/L; serum folate concentration, 14 μg/L; RR, 7.7-24.4 μg/L; pancreatic lipase immunoreactivity, 44 μg/L; RR, 0-200 μg/L; trypsin-like immunoreactivity, 13.3 μg/L; RR, 5.7-45.2 μg/L). Thoracic radiographs disclosed generalized megaesophagus. Additional diagnostic tests to evaluate possible neuromuscular disease were not pursued. The littermate was transitioned to a prescription low-fat intestinal diet and managed by feeding from an elevation, but was lost to follow-up.

5 | DISCUSSION

Here, we report 2 male Labrador retriever littermates with hematologic findings similar to those previously reported in ESS dogs.[13] The ESS dogs were evaluated at 3.5 months or 2 years of age for clinical signs of regurgitation resulting from megaesophagus and generalized muscle atrophy, and hematologic changes identified during the clinical evaluation. By contrast, hematologic changes were identified in the Labrador retrievers at the time of preneuter laboratory testing, and clinical signs of myopathy including megaesophagus only were detected at approximately 5 years of age. Myopathic changes identified in muscle biopsy samples from dog 1 were similar to those reported in the ESS dogs and supported a diagnosis of congenital myopathy with similarities to the centronuclear/myotubular myopathy group of congenial myopathies. The distinct and uncommon pathological changes of dyserythropoiesis and myopathy with excessive numbers of internal nuclei in both breeds suggest a similar underlying pathogenesis, which is not yet characterized but requires further investigation.

The CBC results for both dogs and bone marrow findings for dog 1 are markedly similar to those reported in the ESS dogs. On CBC review, both affected Labrador retrievers had marked inappropriate metarubricytosis and microcytosis, codocytes, rare spherocytes, and schistocytes, all of which were noted in the ESS dogs.[13] A pathologist review of the CBCs performed on both Labrador retrievers when they were young identified microcytosis and inappropriate metarubricytosis. Although splenectomy in dog 1 would be expected to cause some metarubricytosis, this finding was present before surgery. The early identification of the abnormalities, combined with the lack of clinical signs attributable to the erythrocyte abnormalities and extensive diagnostic evaluation, suggests a congenital disorder.

Intramedullary and extramedullary destruction of RBCs has been noted in some forms of dyserythropoiesis,[13] and intramedullary

destruction was noted in the dog evaluated by bone marrow cytology (also noted in ESS dogs). As such, a destructive element to account for the spherocytes cannot be ruled out. However, given lack of progression of the anemia, negative autoagglutination, normal serum bilirubin concentration, and only low numbers of spherocytes, typical immune-mediated destruction was considered less likely. Rather, the finding of spherocytes along with schistocytes, acanthocytes, and keratocytes may indicate increased red cell fragility and fragmentation for the observed changes in morphology. Further investigation would be needed to confirm this suspicion.

The pathological changes in muscle biopsy samples from dog 1 were similar in both the ESS and Labrador retriever dogs, and in Labrador retrievers with XLMTM[8,9] and CNM,[6,7] prompting testing for these mutations. Dog 1 carried the wild type genes. Genotyping was not performed on dog 2. Other mutated genes have been associated with CNM in dogs including BIN1 in Great Danes[11] and DNM2 in Border Collies,[12] but these mutations are not yet confirmed in Labradors.

The prior report of ESS[13] suggested that a mutation in a gene encoding a cytoskeletal membrane protein shared between red cells and muscle, such as spectrin, might account for both hematologic and myopathic changes. Other possibilities include pathogenic variants in genes encoding neuroacanthocytosis syndromes such as McLeod syndrome.[15] McLeod syndrome is a rare and progressive X-linked syndrome in humans resulting from pathogenic variants of the XK gene with widely variable neurologic, neuromuscular, and cardiac manifestations and a distinct hematologic presentation. The XK protein is expressed in many tissues including red cells and muscles and leads to red cell (acanthosis) and myopathic changes (increased central nuclei, increased fiber size variation, and rare degenerating fibers). Pathogenic variants of yet unknown genes shared between red cells and myofibers are still possible. To confirm any of these hypotheses, whole genome sequencing would be required, with a focus on shared or similar genes between muscle and red blood cells.

Variations in clinical presentation among breeds could reflect different genetic backgrounds or the effect of modifying genes. The cardiac abnormalities reported in ESS dogs included right ventricular enlargement in all dogs and right axis deviation in 2 dogs.[13] Dog 1 exhibited a slight right axis deviation (likely normal variation) but did not exhibit any of the other described cardiac abnormalities. An early or mild manifestation of cardiomyopathy cannot be ruled out but is considered unlikely. Cardiac evaluation was not performed in dog 2.

In conclusion, we described a rare, suspected genetic condition of dyserythropoiesis and congenital myopathy without apparent cardiomyopathy in 2 male Labrador retriever littermates. Similar changes have only been reported previously in 3 related ESS dogs (that also had cardiomyopathy). The dogs reported previously all were euthanized before 3 years of age. However, those dogs were not clinically ill before euthanasia. The dogs reported here were 6 years old and clinically doing well but some ongoing muscle atrophy has been noted. The only medical treatment employed was standard management of megaesophagus. These cases provide an additional differential diagnosis for this constellation of clinical and hematologic findings that is less well known and does not appear to severely affect the patient's

quality of life. The impact on longevity has yet to be determined, and follow-up monitoring would be needed to assess disease progression.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Alison Thomas-Hollands https://orcid.org/0000-0002-8093-887X

G. Diane Shelton https://orcid.org/0000-0002-3332-1359

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