Case Report
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Achalasia-Like Disease with Esophageal Pressurization in a Myasthenic Dog

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Key words: Gastroenterology; Gastrointestinal tract; Immunology; Motility and function; Neurology; Neuromuscular disorders.

An 8-year-old, intact male Pug was examined for a 7-day history of progressive weakness, progressive decline in food intake, dysuria, and dysphonia. The dysuria was described as an inability to void when being walked as the dog could not lift its leg and did not urinate although there was evidence of urine leakage in the dog's blankets. When initially examined, the dog was alert with a BCS of 5/9. The physical examination did not reveal abnormalities. Results of hematology, serum biochemistry, and urinalysis as well as abdominal ultrasound did not reveal abnormalities. Upon owners' request, the dog was discharged without further work-up, and gabapentin[a] (5 mg/kg, PO q12h) were prescribed for suspected lumbosacral pain. Because of increasing weakness over the next 2 days, the dog was presented at an emergency clinic, where urinary retention caused by lumbosacral disease was suspected and treated with a single dose of dexamethasone[b] (10 mg IM). Three days later, the dog was again examined for anorexia and progressive weakness. Physical examination revealed an alert dog able to walk 2–3 m with a stiff gate and kyphotic posture before finally lying down.

Laboratory work revealed a CK (111 U/L; reference range, 51–191) within reference range and no abnormalities were detected on urinalysis. A bacterial culture of urine showed no growth. Thoracic radiographs revealed moderate esophageal dilatation and a markedly dilated stomach (Fig 1). Results of a neurologic examination were consistent with a neuromuscular junction disorder, and an edrophonium chloride[c] challenge (0.2 mg/kg IV) showed a dramatic positive response. At the time of electromyographic testing, an upper gastrointestinal endoscopy was also performed because of concerns about steroid-induced gastric ulceration.

Before anesthesia, esophageal high-resolution manometry (HRM) was used to evaluate esophageal function (Fig 2). A manometric catheter was lubricated with 2% lidocaine gel[f] and carefully inserted intranasally. It was passed through the nasopharynx into the esophagus and finally positioned so that it recorded the pressure profile of the entire esophagus from the pharynx to the stomach. Real-time pressure imaging enabled accurate placement, and 3–4 pressure sensors were positioned intragastrically to rule out artifacts caused by breathing-related movements of the esophagogastric junction. HRM examination revealed an abnormal swallowing mechanism: after normal upper esophageal sphincter (UES) relaxation (UES residual pressure 0.4 mmHg [−10.5 to 0.3 mmHg], UES relaxation time to nadir 138 mmHg (58–140 mmHg), relaxation duration 300 ms [145–305 ms]) the aborally propagating peristaltic waves of the tubular esophagus, as well as lower esophageal sphincter (LES) relaxations [LES baseline pressure 37.3 mmHg (14.6–45.1 mmHg), LES residual pressure 27 mmHg (1.9–19.1 mmHg)] were completely absent throughout the study.[1] The peristaltic waves were discontinued by simultaneous contractions of the tubular esophagus beginning at a point just past the first third of the tubular esophagus (Fig 3). The subsequent esophagogastroduodenoscopy did not reveal abnormalities except for a dilated and flaccid esophagus.

Abbreviations:

AChR	acetylcholine receptor
HRM	high-resolution manometry
LES	lower esophageal sphincter
MG	myasthenia gravis

Biopsies were taken from the middle and lower esophagus,[2] stomach, and duodenum. Histopathologically, all esophageal, gastric, and duodenal biopsies did not reveal abnormalities. Electromyographic examination[g] of the limbs and epaxial muscles did not reveal abnormalities. Supramaximal repetitive nerve stimulation of the tibial and ulnar nerve at a frequency of 3 Hz produced a decrement of 30% (reference <10%[3]). At this point, myasthenia gravis (MG) was suspected on the basis of clinical, electromyographic, and pharmacologic testing results. After treatment with pyridostigmin[h] (1.5 mg/kg PO, q8h), the dog had progressive improvement of all clinical findings. By the time the AChR titer came back negative (0.22 nmol/L; normal <0.6 nmol/L)[i] on day 14, the dog had already fully recovered. Upon recheck on day 21, the dog's owners had already stopped pyridostigmin 4 days

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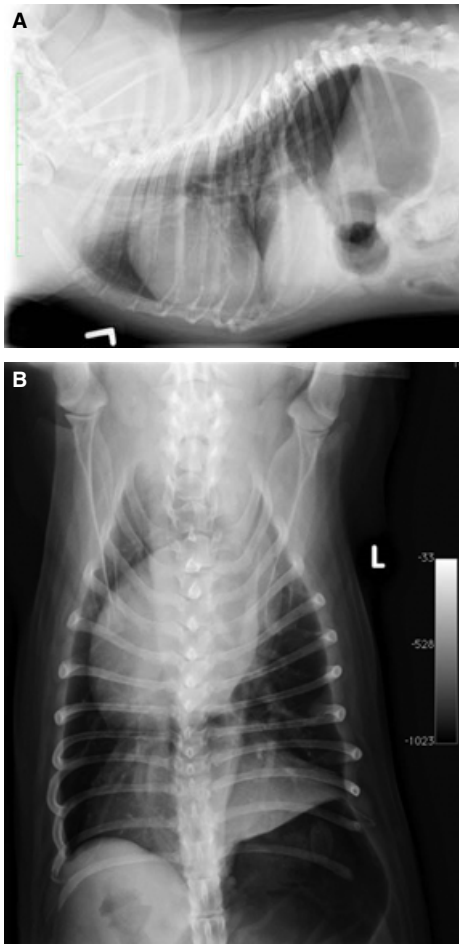

Fig 1. Left lateral (A) and dorsoventral (B) radiographs illustrating a dilated esophagus filled with fluid and gas and a marked gastric distension, filled with a large amount of gas.

previously. Weakness, anorexia, dysphonia, and dysuria had all completely resolved, and the dog appeared bright and alert. The owners agreed to a repeated HRM study of the esophagus that did not reveal abnormalities of esophageal function and swallowing (Fig 4). The dog's clinical signs had not recurred at the time of writing (12 months later).

Discussion

This report describes a dog with an achalasia-like condition of the esophagus caused by MG. Achalasia is associated with functional loss of myenteric plexus ganglion cells in the distal esophagus[4] and is the most well-defined esophageal motility disorder in people where it is characterized by the absence of distal esophageal peristalsis and inadequate LES relaxation.[5,6] Achalasia can be subtyped into 3 groups based on manometric esophageal body pressure profiles. Type 1 is the complete absence of peristaltic contractile activity and minimal pressurization. Type 2 denotes the absence of peristaltic contractile activity with panesophageal pressurization, and type 3 is characterized through spastic esophageal contractions.[6] Histopathologic findings vary in humans with achalasia. The majority of endoscopic esophageal biopsies of achalasic patients are normal,[7] whereas an increased number of intraepithelial lymphocytes is found in patients with primary end-stage achalasia.[8] Our esophageal biopsies comprising epithelium and lamina propria did not reveal abnormalities. This could have been caused by the comparatively acute onset of the disease, or because of the unrepresentative endoscopic biopsies. Another possibility might have been the pretreatment with a high dose of corticosteroids.

After reviewing existing criteria for seronegative MG classification in dogs,[9] we strongly believe the dog

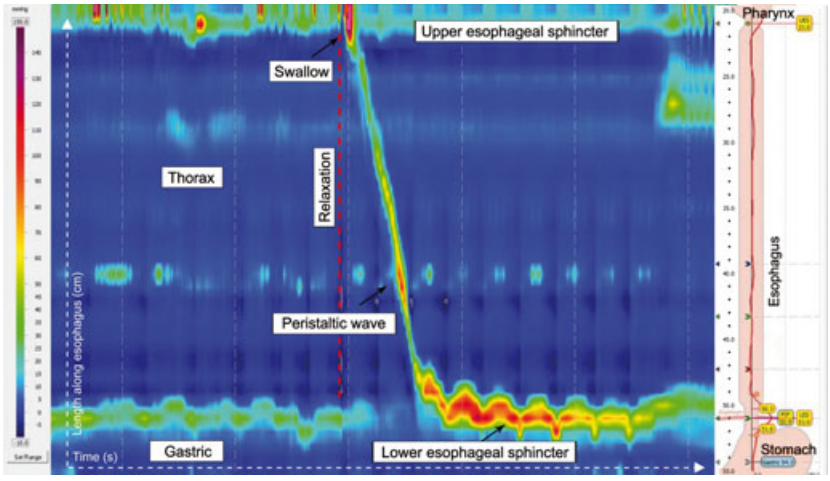

Fig 2. Physiologic swallow pressure topography of a healthy Beagle extending from the pharynx to the stomach, shown in the Manoview software program.[d] Examination was performed with a 36-channel-circumferential solid-state probe with 10-mm spacing between adjacent sensors.[e] The colors reflect the intensity of the pressures; red stands for high and blue for low pressure (color scale on the left side). Upper esophageal sphincter and LES are clearly detectable as high pressure zones. There is a relaxation of both sphincters after a swallow. The figure on the right side shows the schematic position of the catheter in the body. LES, lower esophageal sphincter.

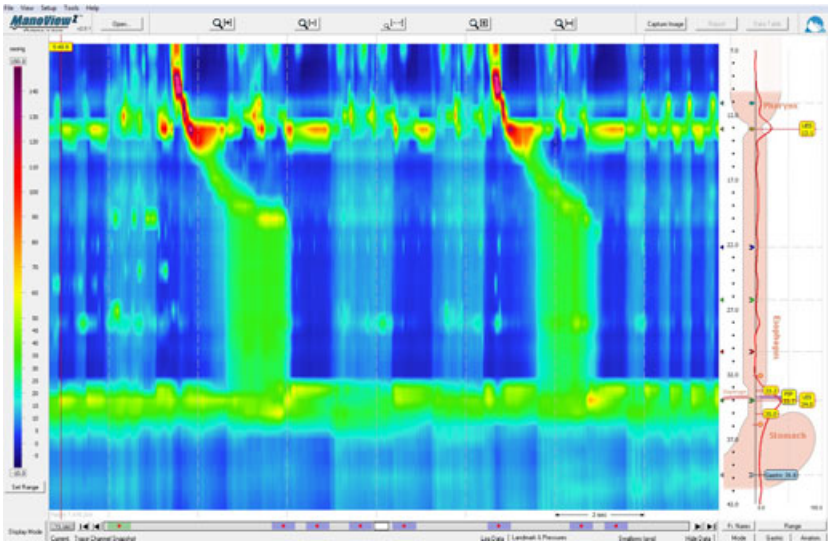

Fig 3. Swallow pressure topography extending from pharynx to stomach shown in the Manoview software program.[d] Examination was performed with a 36-channel-circumferential solid-state probe with 10-mm spacing between adjacent sensors.[e] The 2 swallows demonstrate rapid compartmentalized pressurization extending from the lower two-thirds of the tubular esophagus to the closed LES. No normal peristalsis was seen during the entire manometric examination. (recording speed: 15 s/page). UES, upper esophageal sphincter; LES, lower esophageal sphincter; PIP, pressure inversion point.

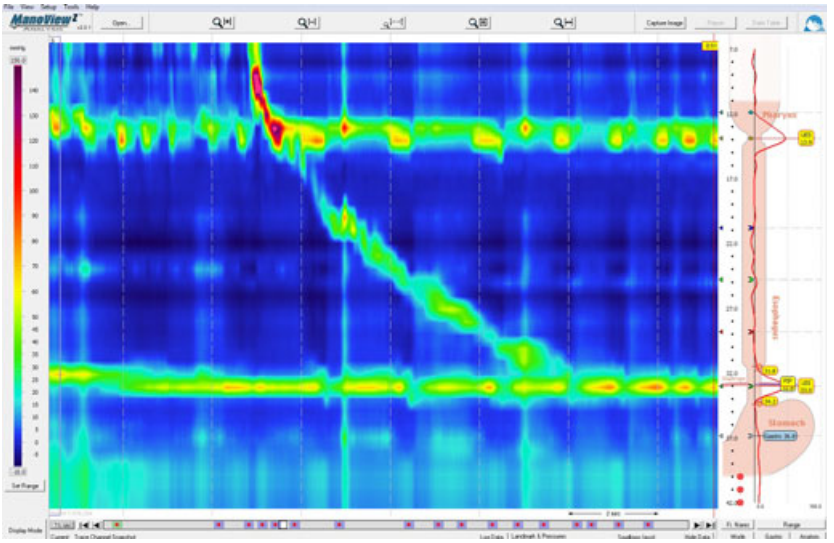

Fig 4. Swallow pressure topography 15 days after the initial abnormal HRM (Fig 3) extending from pharynx to stomach, shown in the Manoview software program.[d] Examination was performed with a 36-channel-circumferential solid-state probe with 10-mm spacing between adjacent sensors.[e] The illustrated swallow represents a physiologic swallow with normal esophageal function. (recording speed: 15 s/page). UES, upper esophageal sphincter; LES, lower esophageal sphincter; PIP, pressure inversion point.

described here had seronegative MG, because of the clinical signs consistent with MG, positive edrophonium response, decremental response of the compound muscle action potential, and normalization of limb muscle weakness after anticholinesterase treatment. In humans, dysuria occurs in myasthenic patients,[10,11] and there is also evidence for this in dogs.[j,12] It has been hypothesized that this is because of autoantibodies directed against ganglionic acetylcholine receptors in the autonomic nervous system.[12] Another explanation would be the existence of both muscarinic[13] and nicotinic antibodies that could have blocked contractions of the detrusor muscle.

Possible explanations for the negative antibody titer result could include the prior treatment with an immunosuppressive dose of corticosteroid medication, early onset of disease with clinical signs preceeding seropositivity causing the titer to rise and become positive upon repeated testing, antibodies directed against non-AChR end-plate determinants, or antibodies

bound to end plates without detectable circulating serum antibodies.[14] It would have been ideal to repeat determination of an AChR titer,[9] but additional samples were not sent because of the rapid response to treatment, and comparatively long turnaround time with overseas shipping. Although less frequently observed, very rapid improvements can be seen with MG in dogs.[k] Further, the complete resolution of all clinical signs is also compatible with an underlying diagnosis of MG.[9]

In humans, HRM constitutes the gold standard for evaluating esophageal function. Utilizing color-coded pressure topography, HRM quickly enables the examiner to obtain an impression of the integrity of the whole swallowing act. Because of the closely spaced pressure sensors, the whole esophagus can be visualized at the same time, from the pharynx to the LES (Fig 2). In addition, HRM is a noninvasive technique, and its feasibility in awake healthy dogs has recently been evaluated by the authors.[1] The unexplained clinical presentation (ie, refusal to eat) together with the suspicion of MG, which can cause dysphagia, provided the indication for manometric assessment of the dog's esophageal function. The HRM findings were consistent with what has been described as achalasia type II with panesophageal pressurization in humans.[15] Strikingly, a similar phenomenon could also be documented in the present case, even though humans and dogs differ in their esophageal muscle composition. Although the entire tubular esophagus is composed of striated muscle in dogs, most of the canine LES consists of smooth muscle.[16] Relaxation of the LES is mediated by a release of acetylcholine from the presynaptic nerve endings, followed by an activation of inhibitory motor neurons.[17] This activation occurs predominantly via nicotinic and muscarinic receptors and the inhibiting neurotransmitter is nitric oxide.[17] In the dog described here, bound AChR antibodies could have led to blocking of the LES relaxation.

The esophagus seems to be able to overcome a closed LES with an adaptive mechanism, the panesophageal pressurization, a condition in which the entire esophageal lumen is pressurized between the 2 sphincters.[18] In humans, achalasia type II patients have aperistalsis, but preserved muscularis propria longitudinal muscle contraction and sufficient excitation of the circular muscle to generate substantial intrabolus pressure in the esophageal body to result in bolus transport.[15] This pressure phenomenon seems to be the major mechanism of esophageal emptying in people suffering from achalasia.[18] Also, in the present case, this mechanism could have allowed the dog to propel ingested food into its stomach. The underlying pathomechanism that triggers the longitudinal muscle contractions has so far not been elucidated in human achalasia. In humans, it is known that the pressurization action is perceived as very painful. It is usually described as a concurrent chest pain.[19,20] We believe this could also explain the anorexia in the dog described in this report. It is possible that refusal to eat was because of the accompanying pain during the act of swallowing. The same observation of painful swallowing occurs in dysphagic myasthenic humans with achalasia.[21–23]

In summary, this is a report of achalasia-like disease secondary to suspected seronegative MG, and clinical recovery from esophageal dysfunction after remission of MG in a dog. Further, this is the first HRM documentation of how esophageal muscles overcome a nonrelaxing LES in dogs. Therefore, it appears conceivable that anorexia in a myasthenic dog might be caused by concomitant esophageal achalasia. In humans with type II achalasia, reasons for chest pain as well as its treatment have not been fully understood.[24] Strategies for treating achalasia comprise medical and surgical options. Pharmacologic treatment with calcium channel blockers, nitrates, phosphodiesterase inhibitors, and botulinum toxin injections may cause prompt reduction in LES pressure, some patients also respond to pneumatic dilations of the LES. Surgical options comprise myotomy and esophagogastric junction stents.[5] Similar strategies against suspected esophageal discomfort in myasthenic dogs with achalasia-like disease have not been investigated so far, but may include pain medication, as well as feeding soft and slurry food until recovery from MG.

Footnotes

[a] Neurontin Pfizer AG, Zürich, Switzerland
[b] Dexadreson MSD Animal Health GmbH, Luzern, Switzerland
[c] Enlon Mylan Institutional LLC, Rockford, IL
[d] ManoViewESO analysis software, Sierra Scientific Instruments (now Given Imaging), Los Angeles, CA
[e] ManoScan ESO Catheter, Small Diameter Regular (EAS), 36 channels with 16 circumferential pressure sensitive segments, 10-mm spacing between sensors, 2.75 mm diameter, Sierra Scientific Instruments (now Given Imaging), Los Angeles, CA
[f] InstillagelAlmed, Farco-Pharma GmbH, Köln, NRW, Germany
[g] NeMus 2+, EB Neuro S.p.A., Florence, Italy
[h] Mestinon, MEDA Pharmaceuticals, Wangen-Brüttisellen, Switzerland
[i] Comparative Neuromuscular Laboratory, University of California, San Diego, CA
[j] Masticatory muscle myositis and myasthenia gravis in a 1.5 year old male Vizsla; Neuromuscular case of the month – October 2004; http://vetneuromuscular.ucsd.edu/cases/2004/oct04.html
[k] Email communication Diane Shelton November 2012

Acknowledgment

Conflict of Interest: Authors disclose no conflict of interest.

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