Jax Wasn't Just Milkin' It

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Introduction

Chylothorax is the accumulation of chyle in the pleural space and it is a relatively uncommon disease in dogs.[10] Chyle typically has a classic "milky" appearance and contains high amounts of triglycerides and lymphocytes. In animals with chylothorax, abnormal flow or pressures in the thoracic duct (TD) lead to exudation of chyle from dilated thoracic lymphatic vessels (aka thoracic lymphangiectasia).[10] This pleural fluid prevents their lungs from expanding and they become dyspneic. Any disease process that disrupts the normal flow of chyle from TD to cranial vena cava (CrVc) can lead to chylothorax, and therefore, countless etiologies must be ruled out.[14] Unfortunately, even with extensive diagnostics, chylothorax is often ruled as idiopathic because an underlying cause cannot be identified. Diagnostics usually consist of thoracic radiographs and/or ultrasound, echocardiogram, thoracocentesis with fluid analysis, +/- thoracic computed tomography (CT).[10,13] If an underlying cause is identified, then the patient should be treated for it in addition to the chylothorax. Surgery is the treatment of choice for idiopathic chylothorax because medical management alone is rarely successful. Medical management typically includes low-fat diet, supplements, and repeat thoracocentesis. Prognosis is dependent upon etiology and tends to vary greatly, but for idiopathic chylothorax it is generally best with TD ligation and subtotal pericardiectomy (SP).[13]

History and Presentation

Jax Droney is a 5-year-old male neutered Doberman Pinscher that originally presented to his primary care veterinarian (rDVM) on July 14th, 2020 for dyspnea while at rest. His only significant health history was that he was taking 0.6 mg of levothyroxine per os (PO) every 12 hours (q12h) for previously diagnosed hypothyroidism. Thoracic radiographs were performed and revealed pleural effusion of unknown origin. A Complete Blood Count (CBC), Chemistry

panel, and Total T4 (tT4) were also performed and were within normal limits (WNL), so Jax was sent home on amoxicillin and furosemide. He returned to the rDVM on July 16th for a thoracic ultrasound and echocardiogram with a mobile imaging service. The echocardiogram showed potential right ventricular systolic dysfunction, and ultrasound revealed a moderate amount of pleural effusion. A thoracocentesis was attempted but was unsuccessful, so the rDVM referred Jax to the Chesapeake Veterinary Referral Center (CVRC), and he arrived at the emergency service (AAVEC) later that day. On presentation, Jax was bright, alert, and responsive. He weighed 65 kg, had a temperature of 100.0 F, pulse of 120 bpm, and was tachypneic. On thoracic auscultation, lung sounds were absent bilaterally and cranioventrally. The remainder of his physical exam (PE) was WNL.

Diagnostic Approach

Diagnosis of chylothorax is confirmed through PE, thoracic radiography and/or ultrasound, and pleural fluid analysis. Thoracic radiographs may reveal pleural fissure lines and/or retraction and "scalloping" of lung lobes with large volumes of effusion.[14] A thoracocentesis may be both diagnostic and therapeutic, and usually yields white or pink opaque "milky" fluid that must be analyzed to confirm chylothorax. On cytology, chylous effusion has a total nucleated cell count (TNCC) of < 7,000/µL and consists of large numbers of small, mature lymphocytes, and lower numbers of nondegenerate neutrophils and macrophages.[11,14] In chronic cases, nondegenerate neutrophils may be more abundant due to inflammation.[11] Biochemical comparison of serum and pleural fluid should include measuring total protein (TP), cholesterol, and most importantly, triglyceride levels. Definitive diagnosis of chylothorax is only made when pleural fluid triglyceride levels are greater than blood serum levels (often $\geq$ 10:1).[11] Cholesterol levels are often lower in pleural fluid and TP is usually 2.5-6.2 g/dL. Chylomicrons in the

effusion will also stain positively with Sudan black stain.[10,11] Once chylothorax is diagnosed, further diagnostic evaluation should be pursued to determine if there's an underlying cause. Diagnostics may include bloodwork, heartworm testing, repeat radiographs following thoracocentesis, thoracic ultrasound and echocardiogram, and CT with or without contrast. Lymphangiography (imaging with contrast in lymphatics) may be performed as well.[10,11,13]

On July 16th, AAVEC recommended Jax have an intravenous (IV) catheter placed, undergo a thoracocentesis with fluid analysis, and repeat radiographs. He was given butorphanol (0.2 mg/kg) IV and the 7th-9th intercostal spaces (ICS) of his left ventral thorax were sterilely prepped. Thoracocentesis yielded ~ 1 liter (L) of milky fluid that was consistent with chylous effusion. The fluid was submitted to IDEXX for analysis, and then thoracic radiographs were performed and submitted for interpretation. A cardiologist at CVRC was consulted and he recommended furosemide be discontinued. Jax was then prescribed gabapentin (10 mg/kg PO q8h) for discomfort and he was discharged with results pending; his owner was also advised to consider consultation with an internist. Later that day, the radiology interpretation revealed pleural effusion was causing retraction of lung lobe margins away from the thoracic wall, and the cardiac silhouette was dorsally elevated, but cardiovascular structures were normal. The report concluded that there was mild to moderate pleural effusion of unknown etiology. On July 17th, the pleural fluid analysis results revealed pink/opaque fluid with a TP of 4.5 g/dL, cholesterol of 107 mg/dL (< blood serum - 150 mg/dL), TNCC of 4,261/µL, and most importantly, a triglyceride level of 2,023 mg/dL. This pleural fluid triglyceride level was 16 times greater than the level measured in Jax's blood serum which was 125 mg/dL (16:1). The fluid had ~ 55% lymphocytes (80-90% small mature), 25% nondegenerate neutrophils, and 20% macrophages; these findings were all consistent with chylous effusion.

Jax re-presented to AAVEC on July 21st (Tuesday) for return of his dyspnea. He was no longer receiving gabapentin as of Sunday (19th), he had one day of amoxicillin left, and he had recently tested negative for heartworm disease. On physical exam, Jax had a temperature of 102.8 F, pulse of 150 bpm, and he was mildly tachypneic with a moderate increase in respiratory effort. On thoracic auscultation, heart sounds were muffled, and lung sounds were dull ventrally. All other PE findings were WNL. A thoracic fast scan (TFAST) confirmed a moderate amount of pleural effusion but no pericardial effusion, and an abdominal fast scan (AFAST) was negative for free fluid. A CBC, Chemistry, and tT4 were sent out, and Jax was given 0.25 mg/kg IV butorphanol and put on flow-by oxygen. Thoracocentesis was then performed and ~ 650 mL of chylous effusion were removed from his thorax. Following the procedure, Jax was monitored until he could be transferred to internal medicine (AVIM) for diagnostics and treatment.

On July 22nd, Jax was transferred to AVIM. His bloodwork had come back, and the only abnormality noted was a mild lymphopenia. The internist recommended that Jax have a cardiology consult; he also recommended that Jax undergo general anesthesia to have bilateral Mila thoracostomy tubes placed to drain fluid from his chest prior to having a thoracic CT performed. The cardiology service (CVCA) performed a thoracic ultrasound and echocardiogram, and they determined that Jax had normal cardiac structure and function with no evidence of underlying cardiac disease or a cardiogenic cause for chylous effusion. Jax was also deemed low risk for cardiac-related complications associated with anesthesia, so he was anesthetized for thoracostomy tube placement. He was placed in left lateral recumbency, his right thorax was sterilely prepped, and a 12-gauge Mila chest tube was placed in the 7th ICS at the costochondral junction. 1.5 liters of chylous effusion were aspirated from the right thorax while Jax was in left lateral and sternal recumbency. The same procedure was repeated on Jax's

left side and an additional 1 liter of chylous effusion was drained from his left thorax. Jax was then moved for a thoracic CT with contrast (89 mL of Omnipaque IV). Jax's CT revealed a moderate volume of bilateral pleural effusion causing multilobar ventral atelectasis, but an underlying structural cause could not be identified. The radiologist also noted prominent sternal lymphadenopathy and cranial mediastinal lymphatic
dilation that likely represented reactive lymphoid hyperplasia. At this time, Jax was diagnosed with idiopathic chylothorax due to a lack of evidence for a cause of his disease.

Pathophysiology

The lymphatic system has three main roles including: maintenance of fluid balance, generation of an immune response, and uptake and transport of dietary fats.[14] The TD is the largest lymphatic vessel in the body, which acts as a conduit for immune cells and lymphatic fluid, and empties into systemic circulation via the CrVc at the lymphaticovenous junction (LVJ).[2,13,14] When fat is digested, it is absorbed by the intestines as chylomicrons which predominantly consist of triglycerides and give intestinal lymph (chyle) its "milky" appearance. From the intestines, chyle normally travels to the cisterna chyli (abdominal lymphatic reservoir), to the TD, and eventually empties into the CrVc.[2,14] However, in animals with chylothorax, there is an abnormality in TD outflow (usually at the LVJ) which leads to leakage of chyle into the thorax. Any disease that increases systemic venous pressures may cause this.[10,14] In addition to pleural effusion, chronic cases can lead to development of fibrosing pleuritis and pericarditis due to the inflammatory nature of chylous effusion.[11,14]

Afghan hounds and Shiba inus may be predisposed to chylothorax.[10,11] Clinical signs are typically associated with pleural effusion and may include tachypnea, dyspnea, exercise intolerance, lethargy, cough, and/or cyanosis. Poor body condition is also seen in chronic cases,

and some patients may have no clinical signs if little effusion is present. Other clinical signs may also be seen with underlying disease. Heart and lung sounds are typically muffled ventrally and bronchovesicular sounds are increased dorsally.[10,11] Fibrosing pleuritis restricts pulmonary expansion and should be suspected in cases where patients' lungs fail to re-expand after thoracocentesis.[11] Bloodwork changes tend to be nonspecific, but some animals will have lymphopenia, hyponatremia, and/or hypokalemia from third-space losses.[10,11] Causes of chylothorax include fungal granuloma, trauma, diaphragmatic hernia, lung lobe torsion, mediastinal or pulmonary neoplasia, jugular vein (v.) or CrVc thrombosis, and ligation of the left brachiocephalic v. or cranial mediastinal veins. Cardiac diseases including pericardial effusion, constrictive pericarditis, heart-based tumors, right ventricular failure, congenital anomalies, dirofilariasis, or cardiomyopathy are also potential causes. Despite this extensive list, the most common diagnosis is idiopathic, which is a diagnosis of exclusion and is usually associated with thoracic lymphangiectasia.[11,14]

Treatment and Management

Treatment of chylothorax is generally subdivided into medical and surgical management. Medical management generally consists of treatment of underlying causes, low-fat diet, rutin (benzopyrone) supplementation, somatostatin analogs, and/or pleural evacuation via thoracocentesis or thoracostomy tube.[10,11] In cases where an underlying disease is diagnosed, the disease should be treated, and effusion should be managed with intermittent thoracocentesis. In most cases, chylous effusion will resolve if the underlying disease is removed; however, resolution may take months.[3] A low-fat diet (1.7-2.5 g/100 kcal) is prescribed to reduce fat molecules in the effusion, which may improve the patient's ability to resorb pleural fluid.[10] Benzopyrone drugs such as rutin (50-100 mg/kg PO q8h) are used to help reduce chylous

effusion. Their proposed mechanisms of action include decreased lymphatic leakage, increased proteolysis, increased macrophage numbers and phagocytosis, and increased resorption of effusion.[3,10,11] Somatostatin analogs (ex. Octreotide) have been used to treat traumatic or post-op chylothorax; these reduce gastrointestinal secretions to aid in healing of the TD by decreasing lymphatic flow.[3,10] Overall, diet modification and supplementation have questionable benefits, but they are still commonly prescribed in animals.[10,11,14] Pleural evacuation may be used initially, but it should not be used chronically. Repeat thoracocentesis can lead to infection, dehydration, lymphocyte depletion, weight loss, and/or loss of lipids, protein, fat-soluble vitamins, and electrolytes. Plus, fibrosing pleuritis and pericarditis may occur due to chronic exposure to chyle.[8,13] To avoid these permanent deleterious consequences, surgical intervention should be pursued if effusion persists greater than 4 weeks.[4] Several studies have revealed that these conservative therapies have a less than 40% success rate in treating idiopathic chylothorax.[3,13]

Surgery is the treatment of choice in cases of idiopathic chylothorax and in patients that don't respond to medical management. In patients with idiopathic chylothorax, TD ligation with subtotal pericardiectomy is the most commonly performed surgical technique. TD ligation can be performed via caudal intercostal thoracotomy (most common), median sternotomy, minimally invasive thoracoscopy, or paracostal or ventral midline celiotomy with transdiaphragmatic extension.[11,13] Adjunctive procedures including SP, cisterna chyli (CC) ablation, and/or thoracic omentalization, have been used to improve success rates of TD ligation. The goal of TD ligation is to occlude the duct at its entry point into the thorax so that new extrapleural lymphaticovenous connections are encouraged to form, which allows chyle to bypass the TD and prevents intrathoracic chyle from leaking into the thorax.[10,13] For TD ligation via caudal intercostal thoracotomy, a 9th or 10th ICS thoracotomy is performed on the right side of dogs. The TD enters

the right side of the thorax at the diaphragm and dives deep at the level of the 6th thoracic vertebra. The TD lies dorsal to the aorta and ventral to the azygous vein and sympathetic chain.[2,13] Ideally, the TD should be ligated as far caudally as possible prior to branching. En bloc ligation involves making an incision in the mediastinal pleura, dissecting tissues ventral and dorsal to the TD, and ligating all tissues between the aorta and sympathetic chain.[13,15] Surgeons can also isolate and ligate the TD and its branches individually. Silk suture and/or hemoclips are typically used for ligation.[10] To help visualize the TD and its branches, patients can be fed cream 3-4 hours prior to surgery, or methylene blue ($\leq$ 0.5 mg/kg) can be injected into a lymph node (mesenteric or popliteal) during surgery.[10,11] Some surgeons recommend post-op imaging to confirm all branches were ligated.[9]

Subtotal pericardiectomy involves removal of a portion of the pericardium ventral to the phrenic nerves.[10] Fossum et al[9] hypothesized that development of a thickened pericardium secondary to chylothorax may lead to increased right-sided venous congestion that could lead to chyle leakage through new lymphaticovenous connections formed after TD ligation. Because of this, TD ligation and SP have been advocated for treatment of idiopathic chylothorax.[13] Several studies have since demonstrated that higher success rates (60-100%) are achievable when TD ligation and SP are combined.[5-7,9] This is compared to success rates of ~ 55% with TD ligation alone.[4,11,13] Thoracic omentalization is another adjunctive procedure that may be beneficial by increasing intrathoracic venous surface area, thereby increasing absorption of effusion; it may also help by sealing leaky lymphatics.[11] Cisterna chyli ablation with TD ligation is less commonly performed, but it may have success rates similar to that of TD ligation with SP. It works by causing rerouting of lymphatic drainage from abdominal lymphatics to the major

abdominal vessels, mesenteric root, or azygous vein.[11] Both thoracic omentalization and CC ablation require an abdominal surgical approach.

At the end of surgery, a thoracostomy tube should be placed so that air and fluid can be aspirated from the chest post-op. Post-op management usually consists of close monitoring, pain management, oxygen supplementation, and aspiration of the thoracostomy tube with recording of outputs. Even if effusion persists, thoracostomy tubes are typically removed or changed within 3 days after surgery.[10,11] Patients are discharged once they are pain free and safe from complications. The most common complication following TD ligation is persistence of chylous or nonchylous effusion (~ 40%), and the post-op period required for formation of effusion to resolve can vary greatly (~1-50 days).[4,10] Other complications may include pneumothorax and lung lobe torsion.[11] As far as prognosis is concerned, several studies have demonstrated short-term success rates of 60-100% with TD ligation and SP, but few studies have evaluated long-term outcome of dogs that have undergone surgery for idiopathic chylothorax.[11,13] With that being said, a recent study[12] reported that 33/39 dogs were free of clinical signs ~ 3 years following video-assisted thoracoscopic TD ligation and SP; and another study[7] reported that 8/11 dogs were free of clinical signs 5 years following TD ligation, SP, and thoracic omentalization. In cases in which surgical therapy has failed or definitive surgical therapy is declined, a pleuroperitoneal shunt or PleuralPort can be considered. An active shunt requires the owner to pump chyle from the pleural to peritoneal space, and the PleuralPort requires them to aspirate pleural fluid from a hub in the subcutaneous tissue.[11,10,13]

Getting back to our patient, Jax's chest tubes were removed the day after his CT (23rd). He was released to go home, and he was started on rutin (50 mg/kg PO q8h) and a low-fat diet. On July 27th, Jax returned for a surgical consultation with CVSS. Thoracic exploratory with TD

ligation and SP were recommended for Jax and he stayed to have surgery the next day. The next morning (28th), Jax was fed cream ~ 3 hours prior to surgery. He was given Cerenia (1.1 mg/kg SQ), placed under general anesthesia (on a ventilator), and he received 22 mg/kg of IV cefazolin. During surgery, a skin incision was made at the right 8th ICS, and a thoracotomy was performed at the 10th ICS. Approximately 1 liter of chylous effusion was encountered as the chest was entered and an additional ~2.2 liters was evacuated via suction. The TD was easily identified with increased fat content, so it was isolated as far caudally as possible and an en bloc TD ligation was performed using large hemoclips. The left hemithorax was opened dorsally while ligating the TD and an additional ~ 800 mL of fluid were removed. Another thoracotomy was then performed at the right 6th ICS, and the SP was performed. No excess fluid was noted within the pericardial sac at time of removal. The ventral 2/3 of the pericardium was removed and saved for histopathology, and the pericardium and chylous effusion were swabbed for culture. A 24 Fr chest tube was placed in the 11th ICS and was sutured in place with Prolene. Next, the ribs, muscles, and subcutaneous layers were each apposed with PDS suture. Following this, 5.3 mg/kg of Nocita (bupivacaine liposome suspension) was injected into tissues around the thoracotomy sites, and the skin was apposed with Monocryl suture. The incision sites were then covered with Telfa and Tegaderm, and air was evacuated from Jax's chest. Post-op radiographs were performed, which showed Jax's chest tube had become kinked, so a 12-gauge Mila chest tube was placed. Once radiographs confirmed proper placement, Jax was fitted with a neoprene chest wrap and moved to the ICU.

Jax's post-op management consisted of dyspnea watch, nasal oxygen, cefazolin (22 mg/kg IV) q8h, Norm R fluids (2.8 mL/kg/hr), fentanyl constant rate infusion (3-5 mcg/kg/hr), aspiration of chest tubes q4h (fluid and air recorded), and chest cold compress q4h. His

levothyroxine, rutin, and low-fat diet were also continued. Three mL/kg/day of air and 40 mL/kg/day of serosanguinous to pink opaque fluid were aspirated from Jax's Mila chest tube in the first 24 hours post-op. The next morning (29th), his 24 Fr chest tube did not appear to be patent, so it was removed. Jax's fentanyl, cefazolin, nasal oxygen, and fluids were discontinued, and he was started on codeine (1 mg/kg PO q8h), carprofen (1.5 mg/kg PO q12h), and cefpodoxime proxetil (9.2 mg/kg PO q24h). Over the next 24 hours, another 25 mL/kg/day of pink opaque effusion was aspirated from Jax's Mila chest tube, but he appeared to be comfortable and was breathing, eating, drinking, urinating, and defecating normally. On the 31st, thoracic culture came back negative, only 6 mL/kg/day of pink opaque effusion was suctioned from Jax's chest, and no fluid was able to be removed after 1 pm that day. On August 1st, Jax's chest tube was removed, and he was discharged later that day with instructions to continue the cefpodoxime proxetil, carprofen, codeine, levothyroxine, rutin, and low-fat diet. He was scheduled for a recheck in two weeks.

Case Outcome

Unfortunately, the night of August 2nd, Jax returned to AAVEC for suddenly looking nauseous, panting, and becoming recumbent. On arrival, Jax was depressed, non-ambulatory, tachycardic (170 bpm), dyspneic, febrile (105.1 F), and he had pale pink mucous membranes and weak femoral pulses. Jax's lung sounds were quieter ventrally, and he was very painful on abdominal palpation. A TFAST revealed mild pleural effusion and AFAST revealed a moderate amount of free fluid. His blood glucose was 105 mg/dL, and pleural fluid was pink/opaque (chylous) with a glucose of 107 mg/dL. An abdominocentesis revealed brown/cloudy fluid with a glucose of 18 mg/dL (87 mg/dL < blood serum) and numerous segmented neutrophils with some containing intracellular cocci. Jax also had a degenerative left shift leukogram with toxic

neutrophils, and a low manual platelet count of 79,000/µL. These findings were consistent with a septic abdomen and systemic inflammatory response syndrome (SIRS). Gastrointestinal perforation was suspected given the nature of Jax's abdominal fluid and how acutely he presented. An exploratory laparotomy was recommended, but given the guarded to poor prognosis, Jax was humanely euthanized and taken home for burial. In the end, Jax's owners didn't elect to submit his pericardium for histopathology and an underlying cause of his chylothorax was never able to be identified. Idiopathic chylothorax was his final diagnosis.

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