Fatty Catty

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Introduction

An approximately 8 month old male neutered domestic shorthair cat presented for circling to the right and loss of balance. The cat would present again over 6 visits during the next 6.5 months for continued neurologic signs and coughing episodes. During these visits, the cat underwent extensive testing after discovering surprisingly lipemic blood samples even after being fasted for 12 hours. The lipemic samples, coughing, and neurologic signs were determined to be due to primary hyperlipidemia due to decreased lipoprotein lipase activity, a condition that has been reported to be heritable in a colony of cats in New Zealand and in related Cheetahs [1, 5].

History and Presentation

Kevin is an approximately 8 month old male neutered domestic shorthair cat that first presented to Mississippi State University Community Veterinary Services (MSU CVS) on April 10, 2017 for circling to the right and loss of balance that began that morning. The owner mentioned that he sneezed once the day before. She also recently bought an essential oil diffuser that Kevin likes to sit and watch. He is up to date on vaccinations and previously tested FIV/ FeLV negative prior to adoption in January 2017. He receives Advantage Multi for cats every 30 days. Physical exam findings were within normal limits except that Kevin exhibited a right head tilt, circling to the right, fast-phase nystagmus to the left, and a delayed menace response. A complete blood count (CBC) and small animal profile (SAP) were performed. The CBC had normal values except for a mild eosinophilia of 1246 /µl (0-1000/µl). However, red blood cell morphology was altered – 1+ anisocytosis, 1+ poikilocytosis, and 1+ echinocytes. The SAP revealed a moderately increased ALP of 91 U/L (10-42 U/L), a mildly decreased globulin of 3.4 g/dl (4.1-6.0 g/dl), and a mildly increased phosphorus of 8.2 mg/dl (2.6-5.7 mg/dl). After several hours at the clinic in a calm environment near a towel sprayed with Feliway, Kevin’s nystagmus resolved and he was able to

walk unassisted. It was recommended that the essential oil diffuser be removed and that the home be examined for irritants such as dusting spray or furniture polish.

On September 6, 2017 Kevin again presented to MSU CVS for worsening coughing. The owner reported that Kevin always had a mild cough since his adoption, but that within the last week, it had gotten significantly worse with extended neck and straining to breathe. Since the previous visit, the owner discontinued use of the oil diffuser and Kevin returned to normal for about two weeks until his signs returned. The owner also reported that one night he was at the foot of her bed and couldn't jump up. He defecated on the rug during this incident, but was back to normal a few hours later so she didn't seek medical attention for Kevin. The owner recently switched from paper litter to clay litter. She Googled some information and read about feline asthma, so she switched back to paper litter on September 5, 2017 (the day before this visit). His diet consisted of two, 6 ounce cans of Nutro wet food. Kevin's physical exam was within normal limits, but a right head tilt was still noted. Thoracic radiographs were recommended with sedation. Prior to sedation and radiographs, a CBC and neuro chemistry panel were performed. The CBC had all normal values except for an eosinophilia of 1847 /µl (normal 0-1000 /µl). The neuro chemistry panel sample was 4+ lipemic, so multiple dilutions had to be completed and it is important to note that glucose, total protein, cholesterol, calcium, and phosphorus are all affected by lipemic sample condition (either falsely increases or decreases values) [2]. Because of the unclear bloodwork results, it was recommended that Kevin be brought back in a few days after fasting for 12 hours so bloodwork could be repeated.

Kevin returned on September 8, 2017 to have a fasted SAP and a urinalysis run. The owner reported that since September 6, 2017, Kevin has only coughed once. She also started giving him a small amount of coconut oil on his food in the mornings. At presentation, Kevin was been

fasted for 12.5 hours. Again, a right head tilt was present on physical exam and the rest of his exam was within normal limits. His fasted blood sample condition was still 4+ lipemic, so his results were still unclear. The urinalysis revealed a specific gravity of 1.028 (slightly decreased from the normal 1.035 in a cat), with no other abnormalities found. Thoracic radiographs were performed and revealed no abnormal findings. At this point, differential diagnoses for Kevin's cough included irritants, parasites (lungworms, heartworms), or infectious etiologies such as mycoplasma infection. The lipemic sample differentials included lipemia secondary to coconut oil administration or hypertriglyceridemia. At this visit, Kevin was prescribed 1.7mls of Fenbendazole (100mg/ml) by mouth once a day for ten days for prophylactic treatment of parasites and 0.3 mls of Doxycycline (50mg/ml) by mouth every 12 hours for 14 days. It was recommended that the owner discontinue coconut oil administration and Kevin return in two weeks to recheck his serum chemistry with another fasted sample.

On September 26, 2017, Kevin returned for his recheck. Kevin's owner reported that the cough got better about one week after starting the medications, but he started to cough (less severe than before) and wheeze again 18 days after beginning the medications. Coconut oil was discontinued on September 9, 2017. Kevin's diet was switched to one 6 ounce can of Nutro canned food, ½ cup Blue Buffalo Wilderness dry food, and about ten Temptations treats per day. The owner reported that Kevin had a great appetite, but he hadn't been gaining weight. On physical exam, Kevin had an increased respiratory rate of 80 breathes/ minute (normal being 20-3 breathes/minute) and still had a right head tilt with possible hypermetric forelimb gait. Kevin coughed once during the day while at the clinic (non-productive harsh cough). The rest of the physical exam was within normal limits. Tests run at this visit included a SAP, bile acids test, total T4, triglycerides, and PLI/TLI/ Cobalamine/ Folate. The small animal profile sample was

not lipemic after being fasted 18 hours and everything was within normal limits except for a mildly increased ALT. The bile acids test sample was 4+ lipemic, and yielded a pre of <4.6 µmol/L (0-12 µmol/L) and a post of 7.1 µmol/L (0-16 µmol/L). The total T4 was within normal limits at 2.4 µg/dl (2-5 µg/dl). Triglycerides were severely increased 673 mg/dl (30-90 mg/dl) using the 4+ lipemic sample. Kevin was prescribed the OM diet which is low in fat (6%) while awaiting send-off test results (PLI/TLI/Cobalamine/Folate). PLI/ TLI/ Cobalamine/ Folate all came back within reference intervals.

Kevin returned on October 10, 2017 for a recheck. Since Kevin's last visit, the owner reported no change in activity or appetite since changing diets to Purina OM, but had added Royal Canin Ultra Light canned food to his diet. Since the last visit, Kevin had some episodes of coughing, however it was overall decreased. The owner also noticed that he had not had as many vestibular/neurologic signs. Kevin's physical exam was within normal limits. At this visit, triglycerides were run pre-heparin and post-heparin administration. A baseline blood sample was taken to check triglyceride levels after the start of the OM diet (started diet 10 days ago). Kevin then received 0.16mL/156IU (45 IU/kg) of heparin intravenously and another blood sample was taken 10 minutes later. The pre-heparin sample (baseline) exhibited 1+ hemolysis and slight lipemia, and yielded moderately elevated triglycerides of 239 mg/dl (30-90 mg/dl). The post-heparin sample exhibited 1+ hemolysis, and triglycerides measured 264 mg/dl (30-90 mg/dl). These results are highly suggestive of primary hyperlipidemia. It was recommended that Kevin only receive OM food. The owner was reminded that it may take four weeks to see the full benefits. A recheck at four weeks post food trial start was scheduled to recheck triglyceride levels.

On November 1, 2017 Kevin returned for his final recheck. Kevin's diet consisted of ½ cup dry OM and 1 can of wet OM. The owner reported that Kevin's cough improved, often going a few days without an episode. His physical exam was within normal limits, except that he appeared thinner than before. A blood sample was taken to determine serum triglyceride levels. His triglycerides were still moderately elevated at 217 mg/dl (30-90 mg/dl). Since his OM diet did not improve his triglyceride levels as much as hoped, he was switched to Hill's Prescription Diet Metabolic + Urinary food which has more omega-3 fatty acids and is higher in calories.

Pathophysiology

Hyperlipidemia in cats can be either physiological (fats mobilized after eating a meal) or pathological. Pathological hyperlipidemia can occur three ways: increased lipoprotein synthesis, increased lipoprotein mobilization, or decreased lipoprotein clearance. Pathological hyperlipidemia can be either primary (genetic/ idiopathic) or secondary to other diseases such as diabetes mellitus, pancreatitis, hyperthyroidism, poor nutrition, hyperadrenocorticism or acromegaly [12]. Kevin was diagnosed with primary pathologic hyperlipidemia due to decreased protein clearance, so we will focus on that pathway.

It is important to first understand normal lipid metabolism. Lipids are fats, and lipoproteins are lipid and protein complexes that are found in plasma. Lipoproteins circulate throughout the body to deliver lipids to specific tissues. There are four classes of lipoproteins – chylomicrons, very low density lipoproteins (VLDLs), low density lipoproteins (LDLs), and high density lipoproteins (HDLs). Chylomicrons are present after a meal and are composed of triglycerides. VLDLs are present during a fasting state and are also composed of triglycerides. Cholesterol is transported as LDLs and HDLs, both of which are present during fasting states. In humans, LDL is considered the "bad" cholesterol that can lead to atherosclerosis. In cats, cholesterol is mostly

transported as HDL (the “good” cholesterol), which is the reason cats rarely have atherosclerosis [7, 12, 13].

Once a meal is consumed, the peristaltic waves of the duodenum, bile, and gastric chyme break down the food to release lipid droplets. Pancreatic colipase binds to these droplets to assist binding to pancreatic lipase. Pancreatic lipase then breaks the lipids into monoglycerides, free fatty acids, and cholesterol. These components are continually mixed with bile to create micelles which can then passively diffuse into enterocytes. Once in the enterocyte, the micelle is deconstructed to access the free fatty acids. The enterocyte uses glycerol and free fatty acids to make triglycerides, then binds the triglycerides to an apolipoprotein to form a chylomicron. At this point, the chylomicrons can enter the plasma and be transported to different parts of the body. Lipoprotein lipase is a very important enzyme that is present in the endothelial cells throughout the vasculature. It functions to breakdown chylomicrons and VLDLs to release free fatty acids for adjacent cells and also acts as a bridge so that the free fatty acids can enter the cells. The remainder of the chylomicron is removed by the liver. VLDL particles are actually leftover fatty acids and remnant chylomicrons that have been processed by the liver. LDLs are VLDLs that have lost fatty acids to cells. HDLs transport cholesterol to the liver for excretion into bile [12, 13].

In Kevin’s case, he is deficient in lipoprotein lipase (LPL) resulting in inefficient clearance of lipids from the serum. In normal cats (LPL +/+), chylomicrons peak in the plasma 3 hours after a fatty meal is consumed and are completely cleared by 7 hours. In cats that are heterozygous for the LPL Gly412Arg mutation (LPL +/-), chylomicrons peak in the plasma at 5 hours and are completely removed by 12 hours. With homozygous LPL mutations (LPL -/-), chylomicrons peak at 7 hours and are not completely removed even after 48 hours. Because lipoprotein lipase

is responsible for the processing of chylomicrons and VLDLs, in LPL deficient cats, triglyceride levels are usually very high (unprocessed) compared to cholesterol which is mostly packaged into HDLs [4]. Kevin was fasted for 18 hours on his September 26, 2018 visit and had a normal sample, so he is likely a heterozygous LPL deficient cat.

Diagnostic Approach/ Considerations

The gross appearance of the serum may be the first finding in a case of hyperlipidemia. In fact, a fasting lipemic sample confirms hypertriglyceridemia. High concentrations of cholesterol do not cause a sample to be lipemic as HDLs and LDLs don't affect serum appearance like chylomicrons and VLDLs do [12].

After the finding of a lipemic sample, it is important to determine whether chylomicrons or VLDLs are causing the sample to be lipemic. A chylomicron test can be performed by collecting a blood sample and allowing the serum to sit in a refrigerator for 12 hours. After this time period, the sample can be assessed. Chylomicrons will float to the top of the sample and form a "creamy layer" while VLDLs will cause the sample to be cloudy. One or both may be increased [12].

Triglycerides and cholesterol concentrations can also be measured which is especially useful in patients that have clinical signs of hyperlipidemia, but no lipemic sample. In cats, a lipemic sample has no effect on cholesterol (unlike dogs) or triglyceride measurements [12]. Cholesterol is already included in MSU's SAP, but triglyceride concentration is an additional test that must be ordered.

Once true lipemia/ hypertriglyceridemia is confirmed, secondary causes should be considered first since primary hyperlipidemia is rare. Tests that should be performed include thyroid function testing for hyperthyroidism, serum pancreatic lipase testing for pancreatitis, and a low

dose dexamethasone suppression test for hyperadrenocorticism. A CBC, serum biochemistry, and urinalysis will help rule in/out diabetes mellitus as well as these other diseases [2, 12].

Primary hyperlipidemia is generally a diagnosis made from ruling out other diseases. However, tests such as lipoprotein electrophoresis and lipoprotein lipase activity are available to confirm suspicions. Lipoprotein electrophoresis is actually a human test so it has limited value in cats since cats have undefined differences in their lipoproteins compared to humans. The lipoprotein lipase activity test can be performed by collecting a baseline serum sample, administering intravenous heparin (45 IU/kg), and then collecting another serum sample 10 minutes after administration. Heparin is known to increase lipoprotein lipase activity causing enhanced chylomicron and VLDL clearance. Triglyceride and cholesterol activity is then measured. If the post-heparin sample exhibits a decrease in triglyceride and cholesterol concentrations compared to the baseline, then lipoprotein lipase functions normally and the animal does not have lipoprotein lipase deficiency [7, 12, 13].

Treatment and Management

Treatment for primary hyperlipidemia is mainly focused on diet modification, with some cases also requiring pharmacologic intervention. It is important to keep in mind that the goal of treatment with these patients is not to reduce triglyceride levels into reference intervals. Instead, emphasis is placed on reducing triglyceride concentrations until clinical signs are minimized. Diets low in fat (<10% or <30g fat/1000kcal) and moderate in protein levels (30% or >85g protein/ 1000kcal) are recommended. Adequate protein is important in these diets because low protein levels can lead to increased serum cholesterol concentrations. When assessing commercial diets, note that the fat content should be low based on metabolizable energy (ME). For example, a diet containing 11% fat with an ME of 4000 kcal/kg provides only 27.5 g

fat/1000 kcal, whereas a diet containing 9% fat with an ME of 3000 kcal/kg provides 30 g fat/1000 kcal. Calorie content essentially doesn't matter. These patients usually have problems with a thin body condition so increasing caloric intake while keeping fat content down is ideal. Treat options should be limited to carrots or brown rice crackers and should only be up to 5% of the daily caloric intake. After four weeks of starting these patients on a reduced-fat diet, reassess plasma triglyceride levels. If the levels have not significantly decreased, a nutritionist may be consulted for advice on an ultra-low-fat home cooked diet or pharmacologic intervention can be introduced [3, 12].

Omega-3 fatty acid supplementation has been proven to be helpful in dogs, and may be beneficial in cats. Fish oil contains a high percentage of eicosapentaenoic acid and docosahexaenoic acid (long chain omega-3 fatty acids). When choosing an omega-3 fatty acid supplementation for cats, be aware that linolenic acid (also an omega-3 fatty acid) is not converted as effectively in cats (including Cheetahs) compared to other species because they have very low delta-6 desaturase activity which is a necessary enzyme to convert linolenic acid to long chain omega-3 fatty acids. Omega-3 fatty acids work to decrease the synthesis of triglycerides and VLDL, stimulate LPL activity, decrease intestinal absorption of lipids, and increase cholesterol secretion into bile [3, 12].

Other agents that may be useful include Gemfibrozil at 10mg/kg BID (which stimulates LPL and decreases production of fatty acids) and beet pulp supplements [3, 12]. Gene therapy is also currently being explored using a human gene coupled with an adenovirus (AAV1-LPL^{S447X}) in LPL -/- male cats. Combined with oral doses of cyclophosphamide (150-200 mg/m^2 per week) to inhibit feline immune response against the humanLPL gene, a dose of 1x10^{11} GC/kg completely

resolved lipemia and hypertriglyceridemia within 7-14 days that lasted for 8 weeks. At week 8, an anti-LPL immune response arose due to cessation of immunosuppressive treatment [10].

Kevin's first therapy included switching him to OM dry cat food from Nutro dry cat food. His Nutro dry cat food diet contained 19% fat. OM dry cat food contains 6% fat with an ME of 3240kcal/kg which provides 18.5 g fat/1000kcal. After four weeks, his triglyceride levels were reassessed yielding a result of 217 mg/dl (30-90 mg/dl). Since his triglyceride levels were not improved as much as hoped and he was losing weight, Kevin was switched to Hill's Prescription Diet Metabolic + Urinary food which has more omega-3 fatty acids and is higher in calories. Hills Metabolic + Urinary feline contains 12.9% fat with an ME of 3289kcal/kg which provides 39.2 g fat/1000kcal.

Case Outcome

Kevin has been staying with his owner's parents in Dallas, Texas since December 2017. He now weighs 7.5lbs and only receives Hill's Metabolic + Urinary wet and dry cat food. His coughing only happens once or twice a day, and he doesn't have full coughing episodes very often. He still has a slight head tilt, but the owner's parents don't report any signs of ataxia. The owner reported in an e-mail that "overall, Kevin is full of energy and seems to be his normal self with no symptoms that are interfering with his everyday life."

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