CASE REPORT
Refeeding syndrome in a cat with hepatic lipidosis

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Refeeding syndrome is characterized by severe hypophosphatemia occurring in patients given enteral or parenteral nutrition after severe weight loss. There are few veterinary reports that describe this syndrome but it is well documented in human medicine. This report describes a case of a domestic shorthair cat diagnosed with hepatic lipidosis following a 4-week history of decreased appetite and weight loss and in whom refeeding syndrome was documented after initiation of enteral nutrition. Clinical findings, blood work abnormalities and disease progression in this patient are described from the time of diagnosis through to recovery. A review of the current literature pertinent to this clinical syndrome is included.

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A 14-year-old, spayed female domestic short-hair cat was presented for evaluation of weight loss and decreased appetite of 4 weeks duration. The patient had been evaluated 8 weeks earlier for intermittent episodes of mixed bowel diarrhea. A minimum database (complete blood count, serum biochemistry, urinanalysis and qualitative fecal flotation) was completed and hypoalbuminemia (2.5 g/dl, reference interval [RI] 3.2–4.7 g/dl) was the only documented abnormality. Abdominal imaging and endoscopy were declined and no definitive diagnosis was established. Nonetheless, resolution was noted following institution of metronidazole therapy and a highly digestible diet (Prescription Diet i/d; Hill’s Pet Nutrition).

On physical examination, the patient was alert and displayed icteric mucous membranes. There was loss of lean tissue, and the body condition score was 1/5. The patient’s body weight (4.22 kg) had decreased 0.9 kg (18%) from the previous visit (5.12 kg). A grade II/VI left, parasternal, systolic heart murmur was auscultated. Pertinent abnormalities from the complete blood count and serum biochemistry are displayed in Table 1. Serum hypocobalaminemia was also documented (<150 ng/l, RI 290–1499 ng/l). Ultrasound-guided liver aspirates demonstrated hepatic lipidosis. Aerobic and anaerobic bacterial cultures of liver aspirates were negative.

The patient was diagnosed with hepatic lipidosis, most likely secondary to gastrointestinal disease. Supportive treatment was instituted with intravenous lactated Ringers solution (LRS; Hospira, 480 ml/24 h), famotidine (Famotidine; Baxter Healthcare, 0.5 mg/kg IV q 24 h), phytonadione (Vitamin K1; MWL 2.5 mg/kg SC q 24 h), s-adenosylmethionine (Denosyl; Nutramax Laboratories, 24 mg/kg PO q 24 h) and mirtazapine (Mirtazapine; Aurobindo, 3.75 mg PO q 72 h). Modest voluntary alimentation was observed, and 3 days after admission an esophageal feeding tube was routinely placed under general anesthesia, using thiopental (Thiopental; Hospira, 13.6 mg/kg IV) and isoflurane (IsoFlo; Abbott Animal Health); the decision to postpone tube placement was made to ensure optimal anesthetic monitoring and support was available in light of the cat’s comorbidities. No immediate post-procedural complications were observed.

The patient’s resting energy requirement (RER) was calculated using the standard formulation, RER (kcal) = 30 × body weight (kg) + 70.1 The patient’s body weight (4.3 kg) at the time of tube placement was employed in this calculation. A canned, high protein, high energy recovery diet (Prescription Diet a/d; Hill’s Pet Nutrition) was provided. The volume of food was increased by 1/3 RER over 3 days to achieve the total RER. The patient was discharged from the hospital 48 h after initiating nutritional support. Over the next 2 days, communications with the owner suggested that the cat was in stable condition.

Three days after discharge, nausea, profuse diarrhea, lethargy and an increased respiratory rate were observed. Upon re-examination, the patient was icteric, tachypneic, markedly depressed, and had generalized muscle weakness. Systolic hypotension (64 mmHg) (Doppler; Parks Medicinal Electrical), relative bradycardia (140 beats per minute) and metabolic acidosis were noted. The patient was rehospitalized in an attempt to stabilize the cat. A repeat serum electrolyte panel revealed hypokalemia (2.7 mEq/l) and hypophosphatemia (2.05 g/dl, RI 2.0–4.5 g/dl).

A second ultrasound examination was performed, which revealed an increased amount of hepatic pathology. Aerobic and anaerobic bacterial cultures of blood were negative. Marked decreases in the patient’s hematocrit (48% to 26%) and total white blood cell count (18,200/μl to 11,000/μl) were noted. A profound decrease in serum albumin (2.1 g/dl, RI 3.2–4.7 g/dl) and globulin (4.9 g/dl, RI 3.0–5.0 g/dl) concentrations were noted.

The patient was placed on ventilatory support and intravenous fluid therapy was initiated. A third ultrasound examination revealed increased amounts of hepatic pathology. An esophageal feeding tube was again placed under general anesthesia, using thiopental (Thiopental; Hospira, 13.6 mg/kg IV) and isoflurane (IsoFlo; Abbott Animal Health).

The patient was placed on mechanical ventilation, and intravenous fluid therapy was initiated. A third ultrasound examination revealed increased amounts of hepatic pathology. An esophageal feeding tube was again placed under general anesthesia, using thiopental (Thiopental; Hospira, 13.6 mg/kg IV) and isoflurane (IsoFlo; Abbott Animal Health).

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per min) with weak femoral pulses and mild hypothermia (98.1°F) were documented. Oxygen responsive hypoxemia (90%) was recorded with pulse oximetry. A moderate normocytic, normochromic anemia and acute inflammatory leukogram with mild toxic change were recorded. Pre-regenerative hemolysis due to oxidative damage or gastrointestinal ulceration was considered a plausible explanation for the anemia as well as anemia of chronic inflammatory disease. Gastrointestinal bacterial translocation, bacterial cholangiohepatitis, and pneumonia were considered for the inflammatory response.

A re-evaluation of serum values (Table 1) suggested differentials for the increasing bilirubinemia. The anemia was characterized by moderate normocytic, normochromic anemia and mild hypochromia. Weight gain (200 g, 5%) and resolution of azotemia were also documented at this time. Although severe lipidosis and other primary liver diseases were initially considered differentials for the increasing bilirubinemia and oxidative damage, the combination of the patient’s nutritional history, hypophosphatemia, hypokalemia and hemolytic anemia was most consistent with a diagnosis of refeeding syndrome. Supplemental phosphorus was provided using potassium phosphate (KPO₄; American Regent). Feeding began at 1/5 RER and was increased gradually over 5 days to achieve the total RER. Approximately 38 h after re-admission, marked hypophosphatemia and hemolytic anemia were recorded (day 10, Table 1). The anemia was characterized by moderate Heinz bodies, basophilic stippling, and occasional polychromasia. Weight gain (200 g, 5%) and resolution of azotemia were also documented at this time. Although severe lipidosis and other primary liver diseases were initially considered differentials for the increasing bilirubinemia and oxidative damage, the combination of the patient’s nutritional history, hypophosphatemia, hypokalemia and hemolytic anemia was most consistent with a diagnosis of refeeding syndrome. Supplemental phosphorus was provided using potassium phosphate (KPO₄; American Regent). Feeding began at 1/5 RER and was increased gradually over 5 days to achieve the total RER. Approximately 38 h after re-admission, marked hypophosphatemia and hemolytic anemia were recorded (day 10, Table 1). The anemia was characterized by moderate Heinz bodies, basophilic stippling, and occasional polychromasia. Weight gain (200 g, 5%) and resolution of azotemia were also documented at this time. Although severe lipidosis and other primary liver diseases were initially considered differentials for the increasing bilirubinemia and oxidative damage, the combination of the patient’s nutritional history, hypophosphatemia, hypokalemia and hemolytic anemia was most consistent with a diagnosis of refeeding syndrome. Supplemental phosphorus was provided using potassium phosphate (KPO₄; American Regent). Feeding began at 1/5 RER and was increased gradually over 5 days to achieve the total RER.

Table 1. Complete blood count and serum biochemistry abnormalities. Values given in bold are outside the RI.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RI</th>
<th>RI*</th>
<th>Day 0</th>
<th>Day 8</th>
<th>Day 9*</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>5.5–19.5 K/µl</td>
<td>–</td>
<td>4.9</td>
<td>25.3</td>
<td>np</td>
<td>10.9</td>
</tr>
<tr>
<td>Hematocrit, spun</td>
<td>30–45%</td>
<td>–</td>
<td>36</td>
<td>22</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Glucose</td>
<td>60–133 mg/dl</td>
<td>70–119 mg/dl</td>
<td>99</td>
<td>303</td>
<td>175*</td>
<td>254</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8–2.1 mg/dl</td>
<td>–</td>
<td>1</td>
<td>1.3</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>16–35 mg/dl</td>
<td>17–37 mg/dl</td>
<td>16</td>
<td>51</td>
<td>17*</td>
<td>9</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2–4.7 g/dl</td>
<td>–</td>
<td>2.8</td>
<td>2.8</td>
<td>np</td>
<td>2.1</td>
</tr>
<tr>
<td>Sodium</td>
<td>150–163 mmol/l</td>
<td>152–162 mmol/l</td>
<td>149</td>
<td>129</td>
<td>136.4*</td>
<td>138</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6–5.5 mmol/l</td>
<td>3.2–5.0 mmol/l</td>
<td>4.4</td>
<td>3.3</td>
<td>3.5*</td>
<td>4.2</td>
</tr>
<tr>
<td>Chloride</td>
<td>116–130 mmol/l</td>
<td>113–126 mmol/l</td>
<td>120</td>
<td>84</td>
<td>108.9*</td>
<td>107</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.7–6.5 mg/dl</td>
<td>–</td>
<td>3.5</td>
<td>6.0</td>
<td>np</td>
<td>1.7</td>
</tr>
<tr>
<td>Magnesium, free</td>
<td>0.77–1.28 mg/dl</td>
<td>0.77–1.28 mg/dl</td>
<td>np</td>
<td>np</td>
<td>1.1*</td>
<td>np</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>45–217 U/l</td>
<td>–</td>
<td>71</td>
<td>76</td>
<td>np</td>
<td>81</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>11–95 U/l</td>
<td>–</td>
<td>607</td>
<td>522</td>
<td>np</td>
<td>490</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0–0.4 mg/dl</td>
<td>–</td>
<td>4.6</td>
<td>10.8</td>
<td>np</td>
<td>8.6</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>75–271 mg/dl</td>
<td>–</td>
<td>168</td>
<td>256</td>
<td>np</td>
<td>196</td>
</tr>
</tbody>
</table>

*Indicates different RI for sample. np = not performed.
inappetence has been recorded; a highly digestible diet was provided at this time (Prescription Diet i/d; Hill’s Pet Nutrition) and the signs resolved in 2 days.

Refeeding syndrome is defined as the constellation of metabolic and physiologic derangements associated with caloric repletion of the starved patient. Classically, refeeding syndrome is characterized by the development of severe hypophosphatemia following the introduction of enteral or parenteral nutrition. Refeeding syndrome can also variably include hypokalemia, hypomagnesemia, vitamin deficiencies, fluid intolerance and glucose intolerance.

It is believed that refeeding syndrome is a consequence of the body’s inability to rapidly adapt from a chronically catabolic state to an anabolic state. Starvation can lead to villous atrophy and compromised absorptive capacity may explain the severe diarrhea observed in the patient described here.

In response to anabolism and heightened by the release of insulin, cellular uptake of phosphorus and inorganic phosphates occurs, leading to hypophosphatemia. Phosphorus and phosphates are required for the synthesis of ATP, DNA, RNA, proteins and 2,3-DPG, as well as for phosphorylation of glucose. Phosphorus depletion leads to a reduction in erythrocyte ATP concentration, failure of actin and myosin, altered erythrocyte membrane lipids and consequently, hemolytic anemia. Heinz body formation contributes to anemia and occurs due to impaired phosphorylation of glucose in the pentose monophosphate pathway. The patient described herein showed evidence of hemolytic anemia and Heinz body formation, and although these changes can result directly from lipodissus and toxin or drug exposure, such etiologies were considered less likely than refeeding syndrome. Additional manifestations of hypophosphatemia may include increased susceptibility to infection, inadequate oxygen delivery to tissues, rhabdomyolysis, impaired diaphragmatic contractility, decreased sarcomere contractility and encephalopathy. Impaired oxygen delivery from anemia and diaphragmatic contractility may have led to this patient’s tachypnea and hypoxemia. In this case, hypophosphatemia was not apparent until 38 h after presentation; however, the presence of a hypophosphatemic state was arguably masked by the reduction in glomerular filtration rate that accompanies volume contraction, which this patient had. This interpretation is supported by the 60% reduction in creatinine that was documented between the value recorded on admission for refeeding syndrome (day 8, Table 1) and the value on the day that volume repletion was accomplished, when hypophosphatemia became biochemically apparent (day 10, Table 1). Ideally, direct estimation of the patient’s glomerular filtration rate would have been conducted to confirm this hypothesis.

The provision of carbohydrates and amino acids to starved patients promotes anabolism and glycolysis leading to intracellular translocation of phosphorus, potassium and magnesium and this is further augmented by the increased release of insulin which is suppressed during states of weight loss and hepatic lipodisosis. For these reasons, a low carbohydrate, high protein and high energy diet is recommended.

Hypokalemia may provoke glucose intolerance, neuromuscular weakness, ileus, polyuria and polydipsia, respiratory depression and cardiac arrhythmias. Our case demonstrated hypokalemia, and this derangement may have contributed to the neuromuscular weakness and respiratory depression observed; this was supported by the notable clinical response to aggressive potassium supplementation. Magnesium is mandatory for cellular processes involving ATP, and hypomagnesemia is an important mediator of hypocalcemia, refractory hypokalemia, cardiac arrhythmias and neuromuscular weakness. Hypomagnesemia is a variable finding in patients with refeeding syndrome.

The remaining electrolyte abnormalities, marked hyponatremia and hypochloremia, were most likely the consequence of electrolyte-rich insensible fluid loss in diarrhea. These abnormalities improved with intravenous fluid therapy; however, more aggressive therapy may have been indicated because such derangements can contribute substantially to generalized weakness.

Thiamine (vitamin B1) is an essential cofactor in a number of reactions involved in carbohydrate metabolism, and it may become depleted when cellular demand increases in response to refeeding with carbohydrates. Thiamine deficiency can be objectively diagnosed by demonstrating deficiencies of erythrocyte transketolase or thiamine-phosphorylated esters; however, thiamine deficiency is more commonly diagnosed by subjectively documenting signs consistent with Wernicke’s encephalopathy and a response to supplementation. Many features of thiamine deficiency-associated-encephalopathy (ataxia, vestibular dysfunction and visual disturbances) are indistinguishable from those induced by hypophosphatemia and hypokalemia, rendering it difficult to define its contribution to refeeding syndrome. It’s important to note that thiamine supplementation is common in commercial pet foods and clinical deficiency is rarely documented in companion animals.

Hyperglycemia documented in patients with refeeding syndrome may reflect the introduction of glucose into a system adapted to fat metabolism. Hyperglycemia can lead to disrupted neutrophil function and hyperosmolar hyperglycemic non-ketotic coma. The cat in this report had only moderate and transient hyperglycemia and although this abnormality was initially attributed to stress it may also be an illustration of the pathophysiology of refeeding syndrome in play.

There is a paucity of reports documenting refeeding syndrome in the veterinary literature, and the incidence is currently unknown. Veterinary literature describing the metabolic complications associated with parenteral feeding is available; however, similar reports focused on enteral nutrition are limited. One publication describes hypophosphatemia associated with enteral alimentation in 2% of feline patients during an 18-month period. To the authors’ knowledge, the three manuscripts that specifically identify refeeding syndrome in
Companion animals are restricted to feline patients. The authors suggest that this may reflect the highly specific nutritional requirements of this species, such as the need for high dietary protein and thiamine as well as essential amino acids. Furthermore, due to their low level of hepatic glucokinase, cats may be more susceptible to the development of hyperglycemia and subsequent insulin release after nutritional support is instituted.

Early identification of patients at risk for refeeding syndrome is a major focus in human nutrition, and experts advocate for correction of electrolyte deficiencies prior to initiating feeding as well as administration of a loading dose of thiamine. When nutritional support is instituted, no greater than 20% of the basal energy expenditure is provided on the first day and supplementation is increased over 4–10 days. Recommended daily monitoring parameters include body weight, urine output, plasma electrolytes, electrocardiographic changes and maintenance of serum glucose within a narrow range.

One veterinary report specifically lists hepatic lipidosis as a risk factor for the development of refeeding syndrome. Interestingly, in the study describing enteral nutrition induced hypophosphatemia in cats, 5/9 cases were diagnosed with hepatic lipidosis. Similarly, humans with cirrhosis and hepatic insufficiency are more likely to develop hypophosphatemia with glucose infusions.

Why the patient in this report developed refeeding syndrome is unknown. The nutritional plan that was implemented adhered to contemporary recommendations not to exceed the patient’s RER and to increase the daily caloric load slowly over 72 h. Perhaps following recommendations from the human literature whereby the patient’s basal energy requirement rather than the RER is used in addition to increasing the daily caloric intake over 4–10 days instead of 3 days, would have prevented this complication. Finally, high risk patients should be identified prior to initiating nutritional support and electrolyte values (potassium, phosphorus, magnesium) and packed red cell volume monitoring should be performed daily until total RER is achieved in order to minimize the risk of refeeding syndrome.

References