# Presumptive Paraneoplastic Syndrome in a Dalmatian with Insulinoma

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Abstract:

This paper discusses the case of a 9 year old, spayed, female Dalmatian who presented with clinical signs consistent with lower motor neuron disease and was diagnosed with presumptive paraneoplastic syndrome secondary to insulinoma. The lower motor neuron clinical signs consisted of moderate to severe, generalized muscle wasting and rapidly progressive generalized weakness over the course of one month. Neurological examination revealed a short-strided gait in all four limbs, tetraparesis, decreased withdrawal reflexes in all four limbs, and collapse if forced to walk without assistance. The clinical signs and examination findings localized the lesion to the neuromuscular system. Initial labwork revealed a hypoglycemia (blood glucose 36 mg/dL), with the remainder of the bloodwork relatively unremarkable. An insulin level was performed, which revealed elevated levels over 200 uIU/mL (ref. 5-20). The clinical signs of lower motor neuron disease were presumptively due to a paraneoplastic syndrome secondary to the insulinoma, as other causes were not definitively ruled out with muscle/nerve biopsies.

Signalment and History:

Gracie is a nine year old, spayed, female Dalmatian that presented to Cornell University's Hospital for Animals Neurology Service on 11/20/2008, with the chief complaint of rapidly progressive weakness and generalized muscle wasting over the previous month prior to presentation. Gracie's owners noticed that she was becoming less active, having more difficulty maneuvering the stairs, and was rapidly losing muscle mass. Gracie was taken to the family veterinarian, after she fell down the stairs and

appeared painful at her back end. The veterinarian also felt that Gracie was painful on palpation of either the lumbosacral or coxofemoral joints, and planned on dispensing a non-steroidal anti-inflammatory (Metacam). Complete blood count and serum chemistry panels were performed, which revealed hypoglycemia (blood glucose 37 mg/dL), with the remaining bloodwork results relatively unremarkable. The referring veterinarian commented on the bloodwork, saying that the blood glucose level was likely an error due to the blood sitting on the counter for an extended period of time before it was analyzed. After about a week of no improvement, Gracie returned to the family veterinarian, at which time a thyroid level was performed, which revealed values within normal limits. Gracie continued to decline, showing further progressive weakness and muscle atrophy consistent with neuromuscular disease, so she was referred to Cornell University's Hospital for Animals for further evaluation.

Chief Complaint and Exam Findings:

Gracie presented to Cornell University's Hospital for Animals Neurology Department on November 20, 2008, with the chief complaint of rapidly progressive generalized weakness and muscle atrophy over the period of about a month. General physical exam revealed severe generalized muscle atrophy and generalized weakness, with difficulty supporting her own body weight. The neurological exam revealed a short strided gait in all four limbs, tetraperesis, and she would quickly collapse if forced to walk more than a few steps. Her spinal reflexes showed decreased withdrawal reflexes in all four limbs. The remainder of the exam was unremarkable.

Problem List and Differentials:

The problem list consisted of generalized weakness, tetraparesis, muscle wasting; all of which was consistent with a neuromuscular disorder. The differentials for lower motor neuron disease included a myopathy of infectious or immune-mediated origin, a neuropathy of immune-mediated, paraneoplastic, metabolic, or idiopathic origin, and neuromuscular junction pathology. More specifically, pathologic agents and disease processes such as Toxoplasma sp., Ricketsia sp., Neospora sp., tick paralysis, Coonhound paralysis, and Myasthenia Gravis were considered.

Diagnostic Plan and Results:

The findings were relayed to the owners and further diagnostics, such as repeated complete blood count (CBC) and serum chemistry panels, 3 view thoracic radiographs and abdominal ultrasound to screen for any metastatic disease, titers for infectious agents (Toxoplasma, Neospora, and Rocky Mountain Spotted Fever), and acetylcholine receptor antibody levels, were discussed. Beyond these, diagnostics such as muscle and nerve biopsies and electrodiagnostics, were discussed as an option to obtain a more definitive diagnosis but the owners opted to initially pursue the bloodwork, radiographs, abdominal ultrasound, and infectious titers. Blood was obtained and submitted for the CBC, Chemistry panel, infectious titers, and acetylcholine receptor antibody levels. The radiographs and abdominal ultrasound were performed while those results were pending, which revealed no indication of metastatic disease on 3-view thoracic radiographs. The abdominal ultrasound revealed a 0.5 cm isoechoic nodule in the spleen and mild mineralization in the kidneys, but no underlying cause for the neuromuscular weakness.

The results from the CBC were unremarkable, and the chemistry panel revealed mildly elevated AST (61 U/L; ref. 16-50) and CK (699 U/L; ref. 58-241), and a hypoglycemia of 36 mg/dL (ref. 60-120).

Updated Differentials, Diagnostics, and Diagnosis:

The hypoglycemia seen on both sets of bloodwork led us to believe that the low blood glucose levels were a real and persistent finding. Differentials for persistent hypoglycemia consist of neoplastic causes, such as insulinoma, hepatocelluar carcinoma, lymphosarcoma, and leiomyosarcoma. Non-neoplastic differentials include hypoadrenocorticism, starvation, sepsis, and end-stage liver failure. Based on the clinical signs and our current diagnostic results, our top differential was a paraneoplastic effect caused by insulinoma. At this time, we requested that an insulin level be performed on the previously submitted serum sample, which revealed levels over 200 uIU/mL (ref. 5-25). After discussing these results with the owners, they opted to cancel the infectious titers that were previously submitted and not pursue muscle/nerve biopsies or electrodiagnostics. The acetylcholine receptor antibody levels revealed results within normal limits. At this time we made a diagnosis of insulinoma, and assumed that the neuromuscular disease was a result of a paraneoplastic syndrome caused from the insulinoma.

Discussion:

In dogs, insulinoma is an uncommon tumor of the pancreatic beta cells, most commonly seen in middle to old aged, medium to large breed dogs. It is the most

common islet cell neoplasia in the dog. In humans, insulinomas are distributed evenly throughout the pancreas, and up to 90% of insulinomas are benign, solitary tumors (3). In dogs, most are malignant (60% carcinomas, the remainder adenomas (4)), solitary, and located in one of the two limbs of the pancreas, rather than in the body (1). The most common sites of metastasis are regional lymph nodes and the liver (1). Insulinoma is an endocrinologically active neoplasia of the pancreatic beta cells, where proliferation of the beta cells causes excessive insulin secretion, leading to hypoglycemia (4). In the normal dog, insulin secretion is completely inhibited when the blood glucose concentration is less than 65-80 mg/dL, but with insulinoma, insulin secretion persists independently from blood glucose concentration (1).

Clinical signs seen with insulinoma manifest as central nervous system signs, such as weakness, collapse, ataxia, disorientation, mental dullness, visual disturbances, and collapse (1,4,5,6). Peripheral polyneuropathies, such as tetraparesis and decreased or absent appendicular reflexes, can be seen (1,6). In the more severe cases, clinical signs such as seizures, coma, and death may occur (1,4,5,6). The clinical signs associated with insulinoma are typically secondary to hypoglycemia and are considered a paraneoplastic phenomenon.

Paraneoplastic syndromes are neoplasm-associated alterations in bodily structure, and/or function that occur distant to the tumor (2). These paraneoplastic syndromes often occur in conjunction with the tumor, therefore, treatment of the tumor often leads to the resolution of the paraneoplastic effects. Recurrence of the paraneoplastic syndrome often indicates the return of the tumor, and many times precedes the gross recurrence of the tumor itself (2). These paraneoplastic syndromes my be present and precede the diagnosis

of the cancer by months to years (7). Paraneoplastic syndromes are variable, and many etiologies are unknown. The exact mechanisms of the various paraneoplastic syndromes are often unknown as well, but they typically are thought to be caused by small molecules released into circulation, which have their effects at distant sites (2). It is important to know about paraneoplastic syndromes and recognize their association to cancer, because various syndromes can lead you to an earlier detection and treatment of specific types of neoplasia.

As in the case with Gracie, an elevated insulin level in the face of hypoglycemia is a very specific diagnostic finding with insulinoma. The paraneoplastic syndrome of hypoglycemia can occur with other neoplastic processes such as hepatocelluar carcinomas, lymphosarcoma, and leiomyosarcoma, but these neoplasias do not cause elevated insulin levels. Other neoplasias have specific paraneoplastic syndromes as well. Gastric ulceration can be seen as a paraneoplastic effect of mast cell tumors. Hypercalcemia, also known as hypercalcemia of malignancy, can be seen with a number of neoplastic processes, but is most commonly associated with lymphosarcoma. It may also be associated with anal sac apocrine gland carcinoma, thyroid carcinoma, multiple myeloma, bone cancers, mammary gland carcinoma/adenocarcinomas, squamous cell carcinoma, thymoma, or parathyroid tumors. Hypertrophic osteopathy is another paraneoplastic syndrome that is most commonly associated with primary lung tumors. Other neoplastic processes that can manifest hypertrophic osteopathy are tumor metastasis to the lungs, urinary bladder rhabdomyosarcoma, and nephroblastoma. Non-neoplastic processes that may manifest hypertrophic osteopathy include heartworm disease, heart disease, focal lung atelectasis, pregnancy, and pneumonia.

Unfortunately, there are many other paraneoplastic syndromes that we do not understand, and they do not help lead us towards any specific disease processes, such as fever of unknown origin and cancer cachexia.

Hypoglycemic neuropathies, such as what we saw with Gracie are not fully understood. Hypoglycemia may cause alterations at both the central nervous system (CNS) and at the peripheral nervous system (PNS). CNS signs of hypoglycemia include irritability, lack of concentration, disruption of cognitive functions, convulsions and unconsciousness or coma. The CNS relies heavily on glucose for normal metabolic function, and pathologic changes include loss of neurons, more obvious in the cerebral cortex and the hippocampus than in the brain stem, cerebellum and spinal cord, myelin damage, and glial changes (6). PNS changes are seen as distal axonopathy, including both degenerative and regenerative events, with motor neurons more vulnerable than sensory neurons (6). Animal experiments have shown that peripheral neuropathies developed in cases of hypoglycemia with normal behavior (6). Theories of pathogenesis in these peripheral neuropathies include hyperinsulin toxicity, metabolic alterations associated with prolonged hypoglycemia, or immune factors (7).

Diagnostics:

Various diagnostics can be used to determine if insulinoma is present, but the most commonly used method, bloodwork, is also the least invasive and least expensive. A full blood panel, consisting of a complete blood count and serum chemistry panel, should be performed in order to rule out any concurrent diseases, but the most significant findings will be a low blood glucose level. Whipple's Triad, which consists of

hypoglycemic symptoms, a blood glucose level of <50 mg/dL, and relief of symptoms following administrations of glucose, is often associated with insulinoma (1,3). There are reports of mild hypokalemia and elevated serum alanine aminotransferase (AST) and alkaline phosphatase (ALP) in association with insulinomas, but many times hypoglycemia is the only remarkable finding (1). Pairing the decreased blood glucose levels on the serum chemistry panel to an insulin level may be diagnostic. Quantification of a single insulin and serum glucose sample is very useful for diagnosing pancreatic beta cell tumors in dogs (4). Dogs with insulinoma do not always have persistent hypoglycemia, so their glucose levels may be within normal limits when measured. If insulinoma is still suspected, a low fructosamine level may be supporting evidence (4).

Other diagnostic methods, such as imaging (ultrasound and CT) may be useful to help determine the presence of insulinoma, but negative results may not be accurate. Endoscopic ultrasound has been used in human medicine, and has shown to be more sensitive than CT by some groups, but is dependent on operator experience, and the site and size of the tumor (3). Insulinomas may not be seen on exploratory surgery, and intraoperative ultrasound (IOUS) is used in human medicine to help visualize non-palpable intrapancreatic insulinomas (3). Abdominal surgery and pancreatic biopsies may be necessary for histopathologic evaluation in order to make a definitive diagnosis of insulinoma.

Treatment options:

An acute hypoglycemic crisis occurs when there is an acute, and large drop in the glucose levels. The cells of the body don't have any time to compensate for the

decreased amounts of energy available. The cells of the central nervous system are usually affected first, leading to the CNS signs mentioned earlier. In an acute hypoglycemic crisis, treatment consists of a slow dextrose bolus (0.5 g/kg I.V. diluted in 0.9% Sodium Chloride at 1:3 ratio), followed by a constant rate infusion (2.5% to 5% in water) (1). Caution needs to be used, as a bolus of dextrose may stimulate insulin secretion, which can lead to a further hypoglycemic crisis. If there is no response to the dextrose bolus and CRI, Dexamethasone and/or a Somatostatin analog can be added to the therapy. If the patient is seizuring, it may be necessary to administer anticonvulsants to the patient until the seizures resolve.

When the hypoglycemia occurs in smaller increments over a longer time period, the body has time to compensate for the lack of glucose, and clinical signs such as peripheral neuropathies, as seen in Gracie, can occur with or without the CNS signs. The treatment of choice in this case is surgical resection of the tumor and its metastasis. A partial pancreatectomy to remove the insulinoma gives the best prognosis for longest survival times (1,4,5,8). If the entire mass cannot be removed, debulking it may improve glycemic control (3,5). Surgery complications can include a transient hyperglycemia, as it may take time for the remaining pancreatic beta cells to produce an appropriate amount of insulin (1,4,5). Diabetes mellitus may be a sequela to surgery, or pancreatitis may occur due to handling the pancreas. If surgery is not an option, medical therapy can be attempted to control the hypoglycemia.

Medical therapy consists of diet modifications, such as more frequent (every 4-6 hours), smaller meals consisting of high protein, fat, and complex carbohydrates, in conjunction with drugs (1,5,8). Popular medical therapy consists of drugs that encourage

glucose production, inhibits cellular uptake of insulin, or inhibits cellular uptake of glucose. The most popular course of therapy is prednisone. Prednisone increases blood glucose by increasing gluconeogenesis and glycogenolysis by the liver, decreases glucose uptake by cells, and stimulates glucagon secretion. If the adverse effects of prednisone are too severe, or if prednisone doesn't work, diazoxide may be considered (either alone or in conjunction with the prednisone) (1,5). Diazoxide decreases insulin secretion, decreases insulin uptake into the cells, and enhances epinephrine-induced glycogenolysis. Another drug, octreotide, is less popular due to variable results (1,9). Octreotide is a long-acting somatostatin analog, which inhibits secretion of insulin. In humans, only 50% of insulinomas respond to a somatostatin analog due to the lack of somatostatin receptors (3). Streptozotocin is a cytotoxic drug that selectively destroys beta cells in the pancreas or metastatic sites. This drug is effective at destroying the tumor cells, but is controversial due to its nephrotoxicity (1,8). This therapy is less popular due to the nephrotoxicity. According to Moore et. al. (2002), streptozotocin can be administered safely to dogs at an appropriate dose (500 mg/m2 every three weeks) when combined with a protocol for induction of diuresis (8).

Outcome:

Our patient, Gracie, went home on a two-week course of antibiotics (doxycycline 200 mg once daily and clindamycin 300 mg twice daily) as empirical treatment for infectious agents, as she was discharged prior to obtaining the CBC and Chemistry results, which revealed the hypoglycemia. Once the hypoglycemia was noted and followed up with a high insulin level, Gracie was then put on an appropriate dose of

diazoxide, and given the instructions to increase the frequency of her meals over the course of the day.

Unfortunately, we have not been able to get in contact with Gracie's owners for any follow-up information. Given the fact that we do not know if there was any improvement of the neuromuscular disease on the diazoxide, we have to give a presumptive diagnosis of a paraneoplastic syndrome caused by the insulinoma. If there was significant improvement with the diazoxide therapy, it would be suggestive that our diagnosis was accurate, but to be certain, we would have to rule out the previously mentioned infectious agents, performed muscle and nerve biopsies, and electrodiagnostics.

# References:


1. Hess, RS. Insulin-Secreting Islet Cell Neoplasia. In: Ettinger, SJ, Feldman EC Textbook of Veterinary Internal Medicine, 6th edition. Missouri: Elsevier Inc. 2005; pp. 1560-1563.
2. Bergman, PJ. Paraneoplastic Syndrome. In: Withrow SJ, MacEwan EG eds. Small Animal Clinical Oncology 3rd edition. Elsevier Health Sciences. 2001; pp 35-53
3. Mullan MH, Gauger PG, Thompson NW. Endocrine tumours of the pancreas: review and recent advances. J. Surg. (2001) 71, 475-482.
4. Polton GA, White RN, Brearley MJ, Eastwood JM. Improved survival in a retrospective cohort of 28 dogs with insulinoma. J. of Small Animal Practice 2007;48, 151-156.
5. Kraje AC. Hypoglycemia and irreversible neurologic complications in a cat with insulinoma. JAVMA 2003, Vol 223, No.6, 812-814
6. Mohseni, Simin. Hypoglycemic neuropathy. Acta Neuropathol 2001; 102, 413-421.
7. Inzana, Karen D. Paraneoplastic neuromuscular disorders. Vet Clin Small Anim 34. 2004. 1453-1467.
8. Moore AS, Nelson RW, Henry CJ, Rassnick KM, Kristal O, Ogilvie GK, Kintzer P. Streptozocin for treatment of pancreatic islet cell tumors in dogs: 17 cases (1989-1999). JAVMA 2002, Vol.221, No.6, 811-818.
9. Robben JH, Van Den Brom WE, Mol JA, Van Haeften TW, Rijnberk A. Effect of Octreotide on plasma concentrations of glucose, insulin, glucagons, growth

hormone, and cortisol in healthy dogs and dogs with insulinoma. Research in Veterinary Science 80 (2006) 25-32.