Common Paraneoplastic Syndromes

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Cancer has many effects on the veterinary patient. One group of syndromes that must be paid particular attention to is the paraneoplastic diseases. These are a group of changes that occur in the body at sites distant from the actual tumor. Paraneoplastic syndromes can affect many different body systems. Paraneoplastic diseases are important to recognize for many reasons. Often the paraneoplastic change is the earliest indication of cancer and, thus, neoplasia must be included on any differential list when typical paraneoplastic changes are found in the routine medical work-up. Paraneoplastic syndromes can also be used as markers of remission. Many of the paraneoplastic changes will disappear when remission is achieved, and will reappear once the period of remission had come to an end. Identification of paraneoplastic changes is also important in that often they must be treated before treatment of the primary disease can occur. Treating the remote effects of cancer will increase quality of life. Although many different paraneoplastic syndromes exist, hypercalcemia, hypoglycemia, cachexia and anemia are the most clinically significant in the veterinary patient. Chronic treatment most commonly involves removal or treatment of the primary or inciting neoplastic process. The acute treatment of these syndromes can occur quickly. Rapid identification and treatment will allow the patient to have a better prognosis and will help to improve quality of life.

Paraneoplastic changes are those that occur in the body in a location distant from the primary tumor. The remote effects of the disease thus result in clinical signs and syndromes, which are important to recognize and treat. Paraneoplastic syndromes are often a first sign or indication of cancer elsewhere in the body. They often parallel the underlying neoplastic process and can lessen or resolve as the primary malignancy is treated. Paraneoplastic disease can complicate treatment because the morbidity of these secondary syndromes may make a patient unfit for the recommended therapy of surgery, radiation, or chemotherapy.[1] The return of a paraneoplastic sign is often the earliest indication to the clinician that the cancer is out of remission.

There are many paraneoplastic syndromes described in the veterinary literature (Table 1). Early identification of the most common of these syndromes will assist in early and rapid diagnosis of the primary neoplastic process, aggressive treatment of the cancer, rapid amelioration of the clinical signs of disease, a more rapid response to antineoplastic therapy, and a speedy return to an excellent quality of life for the patient. The most significant and commonly seen paraneoplastic syndromes are hypercalcemia, hypoglycemia, cancer cachexia, and anemia.

Hypercalcemia is an elevation in serum calcium levels. A calcium level greater than 18 mg/dL must be considered a medical emergency.[2] Cancer is the most common cause of hypercalcemia in animals with lymphoma (T-cell lymphoma), and anal sac apocrine gland adenocarcinoma being the most common neoplastic causes.[2,3] Less common neoplastic causes include multiple myeloma, thyroid carcinoma, and bone tumors.[2] Other causes and considerations for hypercalcemia are laboratory error, acute renal failure, Addison's Disease, osteomyelitis, hyperalbuminemia, and hypervitaminosis D (Table 2). Clinical signs commonly associated with high calcium include polyuria, polydypsia, vomiting, bradycardia, weakness, lethargy, and anorexia (Table 3).[1,2] Identification of hypercalcemia warrants a complete investigation for cancer. The typical work-up would include a complete physical examination, rectal examination, aspiration of enlarged lymph nodes, chest radiographs, bone-marrow aspiration, radiographs of painful bones, and analysis of urine for specific gravity and Bence--Jones proteins.[1-3]

The causes of hypercalcemia of malignancy are varied. Two main mechanisms are responsible for increased calcium. The first is humoral hypercalcemia and is the result of parathyroid (PTH)-related peptide production by the tumor. This peptide is closely related to PTH hormone, and has the same action as PTH to stimulate osteoclastic bone resorption and to increase renal calcium reabsorption. Increased PTH-related peptide levels have been demonstrated in hypercalcemic animals with lymphoma and anal sac apocrine gland adenocarcinoma.[2-4] Tumors also cause local osteolytic reactions, which stimulates osteoclasts and results in hypercalcemia of lytic origin.[3] Osteolytic hypercalcemia is most commonly present with lymphoma and multiple myeloma. A finding of hypercalcemia is a negative prognostic indicator.

Treatment of hypercalcemia has two parallel approaches. Emergency treatment of hypercalcemia must be made to avoid permanent renal damage, tissue damage, or neurological effects. Concurrent treatment of the primary tumor is essential. Often, once the cancer goes into remission, the hypercalcemia will resolve. Emergency treatment of high calcium levels is directed at increasing excretion of calcium by the kidneys and decreasing resorption of bone. The first line of treatment is volume expansion and correction of any level of dehydration, with subsequent support of kidney function. Normal saline (0.9% NaCl) is the fluid of choice. Saline contains no calcium and promotes excretion of calcium by the kidneys.[2,3] The fluid rate should be set to correct dehydration in 18 to 24 hours and at a level to provide adequate diuresis. Care must be taken when providing fluids at rates greater than maintenance in animals with evidence of hemodynamic compromise (heart murmur, cardiomegaly, and hypertension). Once the animal is hydrated,

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TABLE 1. Paraneoplastic Syndromes in Veterinary Medicine[2]

Hypercalcemia	Hypoglycemia
Cachexia	Anemia
Alopecia	GI ulceration
DIC	Thrombocytopenia
Erythrocytosis	Neutrophilic leukocytosis
Glomerulonephritis	Nephrotic syndrome
Flushing	Pemphigus vulgaris
Myasthenia gravis	Peripheral neuropathy
Fever	Hypertrophic osteopathy

furosemide may be used to assist in dropping the calcium further. Furosemide is a loop diuretic and will help to inhibit calcium resorption in the ascending loop of Henle. Furosemide maybe given at an initial dose of 5 mg/kg intravenously and then at 1 to 4 mg/kg every 8 to 24 hours intravenously or orally.[2,5] Close evaluation of calcium levels and electrolytes is essential to titrate the furosemide dose.[6] Corticosteroids can help lower calcium levels by increasing calciuresis, decreasing intestinal absorption of calcium, and decreasing vitamin D metabolism. However, corticosteroids must never be used in cases of undiagnosed neoplasia, as an eventual diagnosis may not be possible and the response to chemotherapy may be decreased.[2]

Hypoglycemia is another common paraneoplastic syndrome. Hypoglycemia is defined as a blood glucose below 80 mg/dL; however, clinical signs of hypoglycemia are not usually seen until the blood glucose level drops below 45 mg/dL,[3] and some reports have suggested tolerance of blood glucose as low as 20 mg/dL.[6] Causes of hypoglycemia include sepsis, neoplasia, starvation, laboratory error, liver disease, and Addison's Disease (Table 4). Paraneoplastic hypoglycemia is most commonly associated with insulinoma in dogs.[2,3,6] Other neoplasia including hepatocellular carcinoma, hemangiosarcoma, melanoma, lymphoma, and multiple myeloma have been associated with hypoglycemia.[2] Clinical signs include weakness, disorientation, seizures, and in severe cases coma and death (Table 5). The severity of the signs depends on how hypoglycemic the animal is, how the long the animal has been hypoglycemic, and the rate of decrease of the blood glucose. Initial signs of hypoglycemia are most closely associated with the nervous system because the brain has little to no glucose storage capacity.

Islet tumors of the pancreas cause hypoglycemia by excess production of insulin. Evaluation of glucose and insulin levels taken together in animals with hypoglycemia secondary to insulinoma demonstrates high insulin levels in the face of severe hypoglycemia. Extra pancreatic (nonislet) tumors have hypoglycemia with concurrent low insulin levels. Proposed mechanisms for hypoglycemia of extra pancreatic tumors include increased and preferential glucose utilization by tumors, and failure of glycogenolysis and decreased gluconeogenesis.[2] Evidence also exists suggesting that nonislet tumors produce an insulin-like growth factor that will decrease glucose in a manner similar to insulin.

TABLE 2. Causes of Hypercalcemia

Neoplasia
Hyperparathyroidism
Renal failure
Hypoadrenocorticism (Addison's Disease)
Lab error
Hyperalbuminemia
Hypervitaminosis D
Osteolysis

TABLE 3. Clinical Signs of Hypercalcemia

Polyuria
Polydypsia
Vomiting
Weakness
Bradycardia
Lethargy
Anorexia

Emergency treatment of the hypoglycemic patient will help to resolve clinical signs quickly, unless the clinical signs have been made worse by the presence of permanent brain damage. Initial treatment with 50% dextrose at a dose of 2 mL/kg intravenously is the standard hypoglycemic crisis treatment.[5,6] High levels of glucose supplement must be avoided in situations where an insulinoma has been diagnosed or is suspected. Sudden pulses of glucose will encourage further endogenous insulin production and will result in progression of the hypoglycemia. Frequent small feedings with a slow constant-rate infusion of 2.5% dextrose intravenously is the most appropriate treatment. This treatment regime will not correct hypoglycemia, but will keep the dog's glucose level above the threshold for the development of clinical signs in most cases.[2] Prednisone (0.25 to 0.5 mg/kg by mouth every 24 hours) may be used because it causes insulin resistance and increases glycogenolysis and gluconeogensis.[2,5] The use of prednisone must be avoided in cases of undiagnosed disease and in cases where the hypoglycemia is paraneoplastic to lymphoma. Treatment of the primary disease is the most important aspect of therapy for the long-term management of hypoglycemia.

Cancer-related cachexia is a relatively common multivarient paraneoplastic syndrome. Cachexia is caused by changes that occur secondary to metabolic processes in the face of proper and adequate nutrition. Cancer patients with cachexia have weakness and fatigue. They often exhibit progressive weight loss, muscle atrophy, and changes in appetite. Blood work will often indicate hypoalbuminemia and anemia. Immune-system function also will become impaired.[3] Cachexia is a negative prognostic indicator and is a common cause of death.

The clinical signs of cachexia are related to alterations in metabolism and to decreased nutrition. Various neoplastic processes affect the metabolism of proteins, fats, and carbohydrates. Protein metabolism is changed, with an increase in the turnover of protein within the body and a concurrent decrease in the synthesis of new protein. This alteration in protein metabolism is termed a negative nitrogen balance. Tumor cells, unlike host cells, are only able to use amino acids as the substrate for gluconeogenesis. Host cells can use amino acids and fatty acids for gluconeogenesis. This is the major reason why significant protein degradation is noted with cachexia.[3]

Alterations in lipid metabolism include increased lipolysis

TABLE 4. Causes of Hypoglycemia

Neoplasia	Lab error
Sepsis	Starvation
Liver failure	Polycythemia
Hyperinsulinism	Glycogen storage disease

TABLE 5. Clinical Signs of Hypoglycemia

Weakness	Disorientation
Seizures	Paresis
Collapse	Lethargy
Polyphagia	Coma
Death	Tremors

and decreased activity of lipoproteinlipase. These changes result in the mobilization of the body's fat reserves, as the animal becomes more energy deprived. Changes in carbohydrate metabolism occur as well, and include an increase in serum lactate and increased insulin resistance. Tumors preferentially use glucose over the needs to the host. Glycolysis is the process by which tumor cells gain access to the energy in glucose. This is an anaerobic process whose end product is lactate. In order for the host to use lactate to derive energy, it must first be converted back to glucose, thus resulting in a negative energy balance for the host.[3] Therefore, through various alterations in metabolism, the tumor will grow at the expense of the host.

Anorexia is another major cause of weight loss in the cancer patient. The pathogenesis of the decrease in appetite is not clear. Chemotherapeutic agents attack all populations of rapidly dividing cells, including those of the gastrointestinal tract. This is one reason why one of the adverse effects of cancer treatment may be anorexia. Another reason for weight loss is a combination of host-tumor competition, decreased nutrient intake, impaired absorption and digestion, adverse effects of treatment and increased energy output by the host.[1] It has been suggested that a diet high in fats and low in carbohydrates may be beneficial, combined with other supportive care (appetite stimulants, gastrointestinal protectants, intravenous fluids); however, more definitive research is needed in this area.[3]

Anemia is a common neoplastic syndrome seen in the veterinary patient. The degree of anemia can vary from very mild to severe. There are several types of anemia most commonly associated with neoplasia (Table 6). Anemia of chronic disease is common. As the primary disease process progresses, there is a decrease in iron metabolism and storage. This, along with an associated decrease in red-blood-cell life span and decreased response of the marrow to a low red-blood-cell count, will contribute to the anemia. On a complete blood count, this anemia is normochromic (normal mean corpuscular hemoglobin concentration) and normocytic (normal mean corpuscular volume). The treatment is to address the primary tumor.[1,3,7]

Immune mediate hemolytic anemia (IMHA) is another cause of anemia.[1,3] Cancer of any sort may be the inciting cause of any immune-mediated disease process. IMHA is the destruction of red blood cells by the immune system. A positive Coomb's Test or positive slide agglutination test diagnoses IMHA. Evaluation of a complete blood count will most often demonstrate the presence of spherocytes and a regenerative anemia. If the immune destruction is at the level of the bone marrow, then a regenerative anemia may not be noted. On the serum chemistry, an increase in bilirubin (unconjugated) may be noted. Many animals with IMHA are icteric. When neoplasia is known to be the inciting cause, the neoplasia must be treated. Even with treatment of the cancer, immune suppression with prednisone alone or prednisone in combination with azathioprine, cyclophosphamide, or cyclosporine may be necessary.[5] Treatment of IHMA induced by neoplasia with immune-suppressive drugs alone is usually unrewarding.

Blood loss associated with bleeding tumors is another major cause of paraneoplastic anemia. Blood loss may be obvious. This would be the case for a bleeding tumor of the skin or a tumor bleeding into the chest or abdominal cavity (such as hemangiosarcoma).[1] Other types of blood loss may be less apparent, such as blood loss into the urinary or gastrointestinal tract. Blood loss in the urine can be noted on routine urine analysis, by dipstick and by microscopic evaluation of the urine sediment. Blood loss into the gastrointestinal tract can be noted as frank blood in the stool for blood lost in the large intestine and rectum. Blood loss into the stomach or small intestine may result in melena or a positive occult blood fecal test. Animals that have bleeding high in the gastrointestinal tract (stomach or small intestine) will digest the blood as it passes along the digestive system. This will result in increased protein digestion and as a result, the blood urea nitrogen (BUN) will be noted to be increased on serum biochemistry. Blood loss anemia is usually hypochromic (low mean corpuscular hemoglobin concentration) and microcytic (low mean corpuscular volume), and may be either regenerative or nonregenerative.[7] Controlling the primary disease is the treatment of choice.

Other less commonly seen causes of anemia in the veterinary cancer patient include a nonregenerative anemia associated with chronic chemotherapy administration. This anemia is mild and usually subclinical and takes many months to develop, due to the long life span of a red blood cell. Serial evaluation of the complete blood count before each administration of chemotherapy will allow the clinician to trace the red-blood-cell count and note any gradual decline. Other uncommon causes of anemia are cancer invasion of the bone marrow and pure red-cell aplasia.[3]

Although treatment of anemia must be targeted at the specific cause of the anemia, very often blood transfusions are necessary. Transfusions may be needed in animals with chronic anemia when the packed cell volume (PCV) drops to between 12% and 14%. Animals with an acute blood loss may require a transfusion if they have an 8% to 12% decrease in the PCV. Blood transfusions are not treatments for the causes of anemia. Essentially blood transfusions are Band-Aids that buy the animal time while waiting for medications, surgery, or other cancer treatment to take effect or be completed. Blood transfusions can be of packed red blood cells or whole blood. Animals who have never received a transfusion are unlikely to experience any type of transfusion reaction. Commercial blood-typing kits are available and the procedure for cross-matching is well described.[8] Typing and cross-matching will provide a higher level of safety when transfusing. As a general guideline, whole blood may be transfused at a dose of 6 to 10 mL per pound of body weight, to a maximum of 10 mL per pound per hour. The transfusion should take place over 4 hours. One ml of whole

TABLE 6. Paraneoplastic Causes of Anemia

Anemia of chronic disease
Immune-mediated hemolytic anemia
Blood-loss anemia
Chronic chemotherapeutic administration
Myelophthisis
Pure red-cell aplasia

blood per pound of body weight would be expected to increase the PCV by 1%. Packed red blood cells can be transfused at a dose of 3 to 5 mL per pound of body weight, to a maximum of 5 mL per pound per hour. The transfusion should be given over 4 hours. One ml of packed red blood cells per pound body weight should increase the PCV by 2%.[9] Care must be taken when giving a transfusion to decrease any maintenance crystalloid solution to avoid volume overload. Evaluation for evidence of transfusion reactions, such as an increase in temperature, urticaria, difficulty breathing, or evidence of anaphylaxis, is essential. Transfusion reactions must be promptly treated with corticosteroids or antihistamines.[10]

Paraneoplastic syndromes are not uncommonly seen in the veterinary patient with neoplasia. These syndromes are very important to recognize early and act on. Often the paraneoplastic syndrome is the earliest indication of the presence of neoplasia. Not only can these remote effects of neoplasia be life threatening, but they also can decrease the animal's overall prognosis and make treatment more difficult. Some neoplastic syndromes, such as hypercalcemia, are valuable markers to clinicians to indicate when cancer has come out of remission. Although there are many different types of neoplastic syndromes, hypercalcemia, hypoglycemia, cachexia, and anemia are the most clinically significant. Identifying, understanding, and treating these syndromes will allow for more effective cancer treatment, and will provide patients with a better quality of life.

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