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Popular Article

Paraneoplastic Syndromes as Early Indicators of Cancer

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Abstract

Cancer does not always begin with a visible lump or tumour. In many cases, the first clues appear in completely different parts of the body such as unexplained changes in blood tests, weight loss, strange skin lesions, or hormonal abnormalities. These abnormal signs are called paraneoplastic syndromes. Because these signs often precede the detection of the primary tumour, they can serve as important early warning indicators for veterinarians. Recognizing such changes during routine clinical evaluation can facilitate earlier diagnosis and improve management of cancer patients.

Introduction

The term paraneoplastic is derived from a Greek words *para*= alongside or near, *neo*= new, and *plasis*=formation. Paraneoplastic syndromes (PNS) are rare clinical conditions resulting from the systemic effects of tumours; they are unrelated to tumour size, invasiveness, or metastasis (Henry, 2019). They represent a heterogeneous group of disorders that arise as non-metastatic complications of malignancy, occurring in locations distinct from the primary tumour. PNS can occur in both small animals and humans, often presenting with similar symptoms (de Souza and Borges, 2018). PNS occur when tumour cells produce hormones, cytokines, immune responses, or other biologically active substances that affect organs distant from the primary tumour. These changes are not caused by the physical presence of the tumour itself (Elliott, 2014). Because few of these syndromes may develop before the tumour becomes detectable, they can sometimes provide the earliest clue that cancer is present in the body.

Classification schemes for PNS vary, but most currently categorized according to body systems: endocrine, neurological, musculocutaneous, hematological, and others (Mellanby, 2011). Although many different paraneoplastic syndromes exist, hypercalcemia,



hypoglycemia, cachexia, and anemia are the most clinically significant in the veterinary patients (Bergman *et al.*, 2013).

This article highlights the most important paraneoplastic syndromes observed in dogs and cats and discusses how recognition of these clinical and laboratory abnormalities can help veterinarians suspect underlying malignancies at an earlier stage, even in clinical settings where advanced imaging facilities may not be readily available.

Endocrine (Hormonal) changes

One of the most important groups of paraneoplastic syndromes involves disturbances in the endocrine or hormonal system. Some tumours gain the ability to produce hormones or hormone-like substances, leading to metabolic disturbances throughout the body. Among the most well-recognized endocrine syndromes in dogs is hypercalcemia of malignancy, a condition in which the calcium level in the blood becomes abnormally high. This occurs when tumour cells produce a substance called parathyroid hormone-related protein (PTHrP), which mimics the action of parathyroid hormone and causes calcium to be mobilized from bones and reabsorbed in the kidneys. Hypercalcemia is frequently associated with tumours such as lymphoma, Apocrine gland anal sac adenocarcinoma, multiple myeloma, and thymoma in dogs; lymphoma and squamous cell carcinoma in cats. Animals presenting with unexplained hypercalcaemia should have serum parathyroid hormone (PTH) concentrations measured. In cases where PTH levels are low or within the normal range, evaluation of PTHrP should be performed, as elevated PTHrP concentrations are highly suggestive of an underlying neoplasm.

Another important hormonal disturbance associated with cancer is hypoglycaemia, or abnormally low blood sugar levels. In dogs, the most common cause of tumour-associated hypoglycaemia is insulinoma, a tumour of the pancreatic islet cells that secretes excessive insulin, but this is a direct effect of cancer. Other tumours such as hepatocellular carcinoma, hemangiosarcoma, lymphoma, and melanoma present hypoglycaemia as PNA, they are called non-islet cell tumours (NICTH). They produce ectopic Insulin-like growth factors. Diagnosis typically involves simultaneous measurement of blood glucose and insulin levels. In insulinoma, insulin secretion is inappropriate and remain elevated despite low blood glucose but for NICTH, both insulin and blood glucose is low.

Blood and Bone Marrow Changes

The development of anemia in cancer patients is often complex and multifactorial. Chronic inflammation caused by tumours leads to the release of cytokines that interfere with red blood cell production in the bone marrow. In addition, certain tumours may directly invade



the bone marrow or trigger immune reactions that destroy circulating red blood cells. In other cases, tumours may cause internal bleeding or mechanical destruction of red blood cells within the bloodstream. Animals presenting with unexplained chronic anemia should undergo hematological evaluation, including a reticulocyte count, to determine whether any anemia present is regenerative or non-regenerative. Further testing should include screening for Immune-Mediated Hemolytic Anemia, which can occur as a paraneoplastic manifestation commonly associated with lymphoid malignancies and haemangiosarcomas. A definitive diagnosis of the underlying neoplastic process is established through bone marrow aspiration demonstrating malignant hematopoietic cells.

Another blood abnormality associated with certain cancers is hypergammaglobulinemia, which refers to excessive production of immunoglobulins in the blood. This condition is commonly associated with tumours of plasma cells and lymphoid tissues, lymphoma, and lymphocytic leukemia. Excess immunoglobulins can make the blood unusually thick, resulting in hyperviscosity. Dogs presenting with lameness or limping should first undergo radiographic examination, where osteolytic bone lesions may be observed in cases of multiple myeloma. Subsequently, CBC, platelet count, serum biochemistry, and urinalysis should be performed with particular attention to renal function, serum calcium levels, and proteinuria. If high urinary protein is detected, testing for Bence Jones proteins should be conducted, and confirmation of diagnosis is achieved through bone marrow aspiration demonstrating plasma cell proliferation.

Coagulation changes

Cancer can also disrupt the body's normal blood clotting mechanisms. One of the most severe paraneoplastic complications is disseminated intravascular coagulation (DIC), a condition in which abnormal clotting occurs throughout the bloodstream. Tumour cells may produce substances that activate the coagulation cascade, leading to the formation of widespread microclots. As clotting factors and platelets are consumed, the patient may subsequently develop severe bleeding tendencies (Consumption coagulopathy). Hemangiosarcoma, a highly vascular tumour commonly seen in dogs, is frequently associated with DIC, although other tumours such as mammary carcinoma, lung tumours, and thyroid carcinoma can also trigger this condition. The diagnosis of DIC is made on the basis of clinical signs of a coagulopathy with laboratory findings of thrombocytopenia with clotting defects like hypo fibrinogenaemia, increased fibrin-degradation products and prolonged activated partial thromboplastin time (aPPT).

Gastroduodenal changes



Paraneoplastic gastrointestinal ulceration occurs indirectly due to the release of ulcerogenic substances from the primary tumour. The tumours most commonly associated with this condition include mast cell tumours, which release histamine, and gastrinomas, which produce excessive gastrin. Animals presenting with chronic or non-healing gastrointestinal ulcers should therefore be evaluated for these neoplasms. Systemic histamine excess can be demonstrated by measuring serum histamine concentrations using immunoassay techniques, whereas determination of fasting serum gastrin concentration remains the primary diagnostic test for gastrinoma.

Skin changes

Cutaneous paraneoplastic syndromes are non-cancerous skin conditions that occur secondary to internal malignancies. These dermatological changes may appear months before the tumour is diagnosed, making them valuable early warning signs. In cats, for example, pancreatic carcinoma and less commonly with biliary carcinoma has been associated with a condition known as feline paraneoplastic alopecia, characterized by sudden symmetrical hair loss and a shiny appearance of the skin. Another condition known as nodular dermatofibrosis occurs primarily in German Shepherd dogs and involves the development of multiple collagenous skin nodules associated with renal cystadenocarcinoma. Most affected dogs present with the primary complaint of non-painful cutaneous nodules, but signs of renal pathology such as haematuria may also be present.

Dogs presented with hyperkeratosis and fissuring of the footpads, in which infectious (fungal, parasitic), hormonal, environmental, or other identifiable etiologies have been excluded, should be evaluated for Superficial Necrolytic Dermatitis also known as hepato cutaneous syndrome. histopathological findings of SND are distinctive and can be strongly suggestive of the diagnosis. The epidermis has a 'red, white and blue' appearance when stained with haematoxylin and eosin. Parakeratotic hyperkeratosis and crusting create the upper eosinophilic layer. Oedema and necrosis of keratinocytes in the stratum spinosum make up the pale middle layer. Hyperplastic basal cells give rise to the deep basophilic layer. In addition, secondary clefting can occur at the level of the devitalized middle layer, which may lead to ulceration. A mixed, inflammatory infiltrate may occupy the dermis. Conditions associated with SND are glucagon-secreting pancreatic tumours, hepatic disease and diabetes mellitus.

Neurological changes



Neurological manifestations of cancer are also possible through immune-mediated mechanisms. In some cases, the immune system produces antibodies against tumour antigens that closely resemble proteins present in the nervous system. This cross-reactivity can lead to damage of neural tissues, resulting in paraneoplastic neurological syndromes. One of the most recognized examples in veterinary medicine is myasthenia gravis (MG), a disorder in which antibodies attack acetylcholine receptors at the neuromuscular junction. Dogs with myasthenia gravis often develop generalized muscle weakness, difficulty swallowing, regurgitation due to megaesophagus, and exercise intolerance. The condition is frequently associated with thymoma, a tumour originating from the thymus gland and has also been reported to occur in association with osteosarcoma and bile duct carcinoma. Detection of circulating autoantibodies against the acetylcholine receptor and 'tensilon test' is supportive of a diagnosis of myasthenia gravis. For diagnosis, it is suggested that antibodies against non-acetylcholine receptor proteins of striated muscle are used as markers for the presence of a thymic epithelial tumour in patients with MG.

Skeletal changes

Another rare but notable paraneoplastic manifestation is hypertrophic osteopathy, a condition characterized by the formation of new bone along the shafts of long bones. This syndrome is often associated with tumours located within the thoracic cavity, wide variety of malignant diseases, including primary and metastatic lung tumours, oesophageal tumours, rhabdomyosarcoma of the bladder, nephroblastomas and liver carcinoma. The exact mechanism is not fully understood, but increased blood flow to the limbs mediated by neural reflexes involving the vagus nerve has been proposed as a contributing factor. Diagnosis is based on identification of typical periosteal reaction on radiographs of the appendicular skeleton; the patient should then be followed up by additional diagnostic tests to identify the thoracic lesion. Hypertrophic osteopathy has only been rarely reported in cats.

Conclusion

Ultimately, paraneoplastic syndromes serve as important diagnostic clues that may reveal hidden cancers. For veterinarians, recognizing these indirect effects of cancer can significantly improve early detection and treatment planning. Although advanced imaging techniques such as radiography, ultrasonography, and computed tomography are valuable in identifying underlying neoplasms, such facilities may not always be available in primary-care veterinary clinics. In these situations, careful clinical evaluation together with simple laboratory investigations can still provide important diagnostic clues, allowing clinicians to



reach a preliminary suspicion of an underlying malignancy before considering exploratory surgery or referral to specialized centres.

Clinical Take-Home Points

- Paraneoplastic syndromes may appear before a tumour is detected.
- Unexplained hypercalcemia, anemia, hypoglycemia, or skin lesions should raise suspicion of cancer.
- Recognizing these early warning signs can lead to earlier diagnosis and better management of cancer patients.

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