ACTA SCIENTIFIC CANCER BIOLOGY

Volume 3 Issue 2 February 2019

Review Article

Paraneoplastic Syndromes - A Challenge in Veterinary Medicine

Nayara Maria Gil Mazzante[1], Paula de Sanctis[2]*, Jéssica Leite Fogaça[3], Michel de Campos Vettorato[3], Cláudia Valéria Seullner Brandão[4] and Noeme Sousa Rocha[1]

[1]Investigative and Comparative Pathology Laboratory, School of Veterinary Medicine and Animal Husbandry, São Paulo State University (UNESP), São Paulo, Brazil

[2]School of Medicine from Botucatu, São Paulo State University (UNESP), São Paulo, Brazil

[3]Department of Animal Reproduction and Veterinary Radiology, School of Veterinary Medicine and Animal Husbandry, São Paulo State University (UNESP), Campus (Botucatu), São Paulo, Brazil

[4]Department of Veterinary Surgery and Anesthesiology, São Paulo State University (UNESP), São Paulo, Brazil

***Corresponding Author:** Paula de Sanctis, School of Medicine from Botucatu, São Paulo State University (UNESP), São Paulo, Brazil.

Received: December 10, 2018; **Published**: January 16, 2019

Abstract

The term paraneoplastic syndromes refer to the signs and symptoms that happen before or during a neoplastic process, which are important to detecting the disease early and choosing an adequate therapy. Although widely recognized in human oncology, these syndromes are yet seldom studied in veterinary medicine. Therefore, this literature review covers the main manifestations of these syndromes to aid in the identification and diagnosis for these diseases, as well as in establishing adequate therapeutic protocols. As such, the review covers all endocrine, renal, mucocutaneous, neurological, hematological and mixed syndromes and aims at drawing attention of veterinary oncologists to these syndromes when examining their patients and contributing to a better understanding of the theme in the field of veterinary oncology.

Keywords: Paraneoplastic Syndromes; Neoplasms; Veterinary Medicine

Introduction

As a rule, the essence of a neoplastic process is the silent disorder in cell growth and differentiation resulting in a nodule or mass, except for those that develop from hematopoietic tissue, such as leukemia. For the latter, observing the syndromes may prove to be a useful tool.

Diagnosis of neoplasms as a rule must be conducted through a specific clinical assessment, i.e., Tumor Nodule and Metastasis (TNM), conventional pathology (i.e. cytopathological and/or histopathological assays, including specific stains and/or immunophenotyping) and molecular pathology [1]. In addition, the patients may be not afflicted only by the disease, but also by several systemic signs and symptoms secondary to the tumor: the paraneoplastic syndromes (PNS), which include significant metabolic dysfunction, immune conflict between tumor and host, as well as complex changes in the structure and function of organs and systems [2-5]. Futhermore, most PNS affect tissues or systems distant from the tumor itself.

Fatigue, pain, dyspnea, nausea, vomiting, anorexia, delirium[2] and weight loss despite a lack of change in the appetite are symptoms cause by substances released by neoplastic cells, such as hormones, peptide hormones, growth factors and cytokines. The paraneoplastic syndromes are classified according to the organ or system affected as endocrine, dermatological, hematological, rheumatological, neurological or mixed syndromes [5].

Although frequently recognized in humans, these clinical alterations also happen in animals, but studies in the field are scarce. This explains the lack of success observed in the chemotherapeutic protocols due to changes in the hematological, biochemical and hemostatic parameters. Therefore, these alterations must be investigated to identify abnormalities, establish the prognosis and treat

the syndrome before conducting other therapeutic procedures as they may present higher morbidity than the tumor itself [6].

Therefore, understanding the types of paraneoplastic syndromes and their causes is a key step in the early detection of these diseases and in choosing adequate therapies given that they can be detected before clinical manifestations. This literature review covers the main manifestations observed in cases of paraneoplastic syndromes and aims at aiding in the identification, diagnosis and treatment of these diseases. The databases employed in the review were *Scielo,* Lilacs, Pub-Med-NCBI and BMC.

Body Mass Alterations

Nutrition plays a key role in developing the treatment of cancer patients and, as such, it is paramount to identify clinical signs and symptoms related to malnutrition, such as nausea, diarrhea, vomiting, hard-to-heal wounds, mucositis, proteinuria, constipation, fluid and electrolyte imbalance, weakness, sensory changes in taste and smell, pain, depression and [7-10]. These symptoms lead to a reduction in nutrient intake and anorexia or progressive weight loss despite adequate nutrient intake [7,8,10]. The loss of body mass in cancer patients depends on catabolic mediators and inflammation but is caused by the progression of the disease itself in the case of neoplasms that cause vomiting or increases in tumor mass, which leads in a competition between tumor and host for energy. These symptoms manifest particularly often in tumors afflicting the head and neck, liver, lungs, stomach, pancreas and colon [7,8,10-12]. Tumors located in the abdomen or gastrointestinal tract may lead to a mechanical obstruction and impair organ function, resulting in varied collateral effects such as insufficient digestive secretions and abdominal pain [8,10].

The Body Mass Index (BMI) - for humans - is employed during triage to identify possible weight-related problems in the patients [10], who may be malnourished before the treatment despite following an adequate diet [7]. Additional assessments include the measurement of the tricipital and subscapular skinfolds, dietary evaluation, physical activity and family history [7,10]. These assessments are important because cancer patients may suffer from direct or indirect adverse effects in their nutritional state due to the therapy (surgery, chemotherapy or radiotherapy), 20% of which pass away if the injury is not corrected [8,10,13].

The loss of body mass in these patients is more than a mere aesthetic issue as the situation may prevent patients from continuing the adequate treatment. Therefore, one way to reduce sensory changes in taste and food aversion in veterinary medicine is using glass or porcelain containers instead of metal to reduce the "metallic taste" associated with chemotherapeutic agents, something which has also been reported in humans [8].

Another way to improve the condition of these animals is assisted feeding to ensure an adequate food intake. This process may require the use of food supplements and, in some cases, hospitalization [8]. For patients with cachexia, the diet includes soluble carbohydrates, fibers, fat, fatty acids and omega 3 [12]. These patients present intense muscle and fat tissue expenditure, as well as weakness [12-14]. When the oral nutritional therapy proves to be insufficient, enteral or parenteral nutrition is recommended through a nasogastric tube, gastrotomy or jejunostomy according to the functioning of the gastrointestinal tract [7,13].

Solomon and Garcia (2017) [14] have shown that anamorelin hydrochloride (anamorelin), a synthetic mimetic of the N-terminal active core of ghrelin, when administered to patients with cancer in advanced stages, reduces the loss of body mass by reducing the frequency of nausea and vomiting episodes, thus improving appetite. This substance is already used in animals but is still under investigated as an adjutant therapy.

On the other hand, obesity is also a concern and these animals are predisposed to developing osteoarthritis, diabetes *mellitus* and certain types of neoplasms, in addition to contributing towards a bad prognosis [15-17]. The condition in which excess body fat develops to the point of affecting the animal's health is called obesity [18]. According to Ryan and Kahan (2018) [19], obesity is a complex and chronic disease that should be monitored throughout the patient's life since adipose tissue is involved in energy balancing, lipid metabolism and insulin regulation.

In addition, it acts as an active endocrine organ that secretes several hormones, such as adipokines, one of the most abundant proteins secreted by the tissue [20,21]. This protein, which is a hormone that regulates cell growth and presents anti-inflammatory properties, is negatively correlated to the BMI [22-23]. Significant reductions in the levels of this protein are associated to the relationship between obesity and the developing cancer. Obesity has also been reported as a risk factor for cancer, although the relationship is still not fully understood [24-27].

Hormonal alterations and chronic inflammation also create a favorable environment for tumor progression [24,25]. It has been noted that, within a period of 5 years (2007-2011) in the USA, the incidence of obesity has increased in cats and dogs [26]. It is also

known that obesity influences the incidence of mammary neoplasms in dogs. Pascoli., *et al.* [27] observed, in a study with 11 dogs, the presence of mammary tumors in 15.31% of the animals, of which 29.41% had a body score considered normal, 41.18% were above the ideal weight and 29.41% were obese.

Young dogs tend to present higher energy expenditure due to the anabolic processes inherent to growth while older dogs tend to present lower energy expenditure, storing energy in the form of fat. On the other hand, there is a loss of muscle mass due to the anabolic insufficiency and atrophy caused by the aging process. Adult obese dogs do not become old obese dogs due to the harmful effect obesity has over the animal's longevity. Therefore, obese animals may have a shorter lifespan due to complications arising from excess body fat.

Among these complications, common issues observed include locomotion and articular problems, respiratory and circulatory problems, digestive disorders, as well as endocrine and metabolic alterations such as diabetes *mellitus* and dyslipidemia [28]. Given the prevalence of overweight young dogs, monitoring the animal's body becomes important upon the administration of the first vaccines and should ideally continue throughout the initial stages of the animal's life [29].

Hematological Alterations

Laboratorial alterations of paraneoplastic nature have been identified in several types of tumors, but there are few studies correlating these findings with tumor staging in veterinary medicine [6]. Hematological alterations maybe directly related to the tumor or to the systemic alterations caused by it. A full blood count is a low-cost assay which is essential to assess the patient's clinical profile and select an adequate therapy [30].

Among these alterations, leukocytosis was observed in patients with lung cancer, who present leukocyte counts exceeding 100.000 (hyperleukocytosis). In addition, these patients often present PNSs such as anemia and thrombocytosis, which are associated to worsened prognoses. Patients undergoing chemotherapy with gemcitabine and cisplatin may present leukocytosis with high lymphocyte counts [31].

Another common alteration in veterinary medicine is anemia. It is related to iron metabolism disorders, low counts of bone marrow erythroid progenitor cells, relative erythropoietin insufficiency and elevated levels of inflammatory cytokines. This paraneoplastic syndrome is often observed in cases of lung cancer, head and neck cancer, prostate cancer, multiple myeloma and lymphoma, with patients presenting bad prognoses [2,32-34].

The hemolytic microangiopathic anemia, a rare and fatal form of anemia, is often associated with cancer, being characterized by thrombocytopenia, neurological alterations, kidney failure and fever. It is observed mainly in patients with advanced cancers, including breast cancer, prostate cancer, stomach cancer and lung cancer, being twice more prevalent in women than in men. However, it is still unknown whether this gender difference is the same for animals with similar diseases, representing a possible avenue for further research. The physiopathology of this syndrome is still not fully understood, but it is known that it is distinct from the thrombotic thrombocytopenic purpura, from the hemolytic uremic syndrome and from disseminated intravascular coagulation associated with cancer [35,36].

Another common syndrome afflicting cancer patient is thrombocytosis, which is characterized by platelet counts exceeding 450.000 per cubic millimeter. It is associated with unfavorable prognoses in several neoplasms, such as ovarian cancer, kidney cancer and stomach cancer because platelets promote tumor growth and progression to regulate and maintain angiogenesis [33,37-40]. There is evidence suggesting that tumor cells secrete humoral factors that may lead to thrombocytosis through increased synthesis and activation of platelets, creating a positive feedback to promote its growth [37,38].

Another example is paraneoplastic eosinophilia, in which the absolute eosinophil count exceeds 500 per cubic millimeter of peripheral blood. This syndrome, only rarely reported in veterinary medicine, is caused by an imbalance between eosinophil production in the bone marrow the rolling, adhesion, postcapillary migration and apoptosis [41-43].

In addition, it may lead to complications in malignant hematopoietic tumors and in cases of lung, stomach and kidney cancer. The physiopathology of this syndrome is still not fully understood, but it is believed that interleukins IL-3 and IL-5 are involved in the differentiation and maturation of the eosinophils [45].

Some types of cancer may have several syndromes associated with them, such as lymphoma, which represents 5% to 10% of all neoplasms afflicting canines. Anemia, lymphocytosis, neutrophilia, leukocytosis, leucopenia and thrombocytopenia are often associated with lymphomas and the first two syndromes represent an

indication for bone marrow biopsy, which is important for staging this disease [31].

Other common syndromes afflicting cancer patients included high blood pressure and the Paraneoplastic Acral Vascular Syndrome (PAVS). High blood pressure, for instance, has be reported by Balia., *et al.* [45] in a case of primary ciliary body carcinoma and it is known that PNSs that may cause systemic high blood pressure are probably associated with hepatocellular carcinomas or kidney neoplasms. On the other hand, the PAVS is a rare phenomenon observed in adenocarcinomas that is clinically similar to Raynaud's phenomenon, but is characterized by ischemia and necrosis affecting mainly the hands [45,46].

Endocrine Syndromes

The endocrine system is one of the most commonly affected by neoplastic syndromes, which are often the result of the tumor releasing of hormones, cytokines, peptides and amines leading to metabolic disorders [5,36,47-49]. These syndromes are usually detected after the diagnosis of cancer and the most common of them, both in small animals and humans, is hypercalcemia, which is characterized by high serum concentrations of calcium due to neoplastic processes and which is related to worsened prognoses.

This paraneoplastic syndrome may be secondary to bone destruction caused by the development of bone neoplasms or be caused by the ectopic synthesis of parathyroid hormone-related protein, which happens more frequently in squamous cell tumors or when the PTH-related peptide is secreted erratically, which leads to increases in the serum levels of calcium and phosphate [5,36,47,49-51]. It may be classified as mild (12-15 mg/dL), moderate (15-18 mg/dL) or acute (exceeding 18 mg/dL) [5,36].

In dogs, the syndrome has been reported in 40% of the cases of lymphoma and has also been observed in cases of multiple myeloma, apocrine gland carcinoma, mammary cancer and lymphomas, in which it is caused by the release of vitamin D. It occurs less commonly in cases of seminoma, thyroid carcinomas, bronchogenic carcinomas, squamous cell carcinoma, nose carcinoma, ovarian carcinoma, rectum carcinoma prostate carcinoma and pancreas carcinoma [36,47-49]. Its persistence may lead to kidney failure caused by reduced glomerular filtration, as well as vomiting, hyposthenuria, dehydration and polydipsia [4,47,49-51].

Calcium also affects the gastrointestinal, cardiovascular and neurologic systems directly, leading to anorexia, constipation, bradycardia, high blood pressure, weakness of the skeletal muscles, mental disorders, comma and seizures. The treatment must consider the results of laboratorial tests, some patients do not require aggressive therapies [36,47,49-50]. Correcting fluid deficits and establishing a diuretic therapy with furosemide and glucocorticoids are among the commonly adopted treatments [49].

Another PNS afflicting the endocrine system is Cushing's Syndrome, which is caused by the ectopic production of Adrenocorticotropic Hormone (ACTH) or Corticotropin-Releasing Hormone (CRH) by tumor cells. Around 50 to 60% of the cases are neuroendocrine. Clinical manifestations cause hyperglycemia, hypokalemia, high blood pressure, hypocalcemia, general edema, proximal muscle atrophy, general skin atrophy and reduced bone density. This syndrome is more frequently observed in cases of pancreas cancer, small-cell lung carcinoma, bronchogenic carcinoma and neuroendocrine tumors [5,47,48].

Laboratory test results associated with the syndrome include base cortisol levels exceeding 29 µg/dL, urine free cortisol levels exceeding 47 µg/24 hs and midnight ACTH levels exceeding 100 ng/L. Antihypertensive and diuretic agents may, with adequate monitoring of serum potassium levels, be employed to control the symptoms [47].

Hypoglycemia has also been observed, although less frequently. Its physiopathogenesis may be associated to the inhibition of counterregulatory hormones and changes in the sensitivity of insulin receptors. In small animals, the glucose levels observed in the blood are below 70 mg/dL and the main types of cancer associated are plasmacytomas, lymphomas, leiomyosarcomas, oral melanomas, hemangiosarcomas, salivary gland adenocarcinomas and less frequently in mammary carcinomas. In addition, clinical manifestations include weakness, disorientation, muscle tremors, tachycardia, paresis, seizures and comma [36,49].

Diagnosing this syndrome involves measuring blood sugar levels and identifying the underlying neoplasm through laboratory and imaging tests, such as radiographies, ultrasound, CT scan and MRI. The treatment consists in maintaining blood sugar levels, which can be achieved with small dosages of prednisone or octreotide subcutaneously, as well as through a diet rich in fibers and complex carbohydrates, moderate protein intake and low fat and sugar intake [49].

Another common syndrome is the inappropriate secretion of antidiuretic hormone (ISADH), which afflicts 1% to 2% of cancer patients and is characterized by hyponatremia and secretion of

ADH by tumor cells. Clinical manifestations include nausea, weakness and headaches. Characteristics suggesting this diagnosis included urine sodium levels exceeding 40 mmol/L or osmolality exceeding 100 mOsm/kg of water when the thyroid is functioning normally, and serum cortisol levels are normal. This paraneoplastic syndrome has been associated more frequently with small-cell lung cancer, but has also been observed in cases of esophagus, stomach, pancreas, duodenum, colon and rectum cancer [5,47].

Hyperestrogenism afflicts 20% to 30% of dogs with sertolioma and is characterized by feminization syndrome, including penile atrophy, squamous metaplasia of the prostate, pendulous foreskin and gynecomastia, the latter caused by the synthesis of chorionic gonadotropin (hCG) and high estrogen production. In humans, excessive hCG levels have been observed in cases of mammary tumors, gastrointestinal tract tumors, melanomas and ovarian or testicular cancer, such as seminomas. The diagnosis is reached based on anamnesis, full blood count, myelogram, histopathological assays and plasma or serum estrogen dosage tests [49,52].

Cutaneous Manifestations of Cancer

The cutaneous manifestations of cancer may be physiologically classified as direct effects when they are the result of invasive tumor masses or metastatic dissemination; or indirect effects, which are also called paraneoplastic syndromes. A dermatologic injury is considered paraneoplastic when associated to a cancer in a frequency that gives its presence significance; when it happens before, during or after the diagnosis of cancer; and when it improves after the cancer is successfully excised [52].

Ramos-e-Silva., *et al.* [53] described the dermatologists being familiar with the main paraneoplastic syndromes in humans contributes towards identifying the issue and reaching an early diagnosis, often leading to better prognoses. The authors agree with Silva., *et al.* [54], who attributed better prognoses to patients diagnosed at initial stages of the disease, highlighting the importance of analyzing the clinical manifestations of each condition and understanding their pathogenesis.

Therefore, coexistence with a dermatological disorder may be a first diagnostic indicator for underlying malignancy in seemingly healthy patients, possibly leading to a diagnosis of the tumor and the establishment of a therapy [53]. Stone and Buescher (2005) [55] discussed the relationship between malignancy and dermatological disorders, as well as the mechanisms through which they happen, reaching the conclusion that patients complaining about inexplainable itches should be tested for hidden malignancy.

Skin metastases, for example, may indicate that the malignant tumor has not been eradicated and point towards the recurrence of a primary tumor [53]. Turek (2003) [56] reported cases of paraneoplastic dermatoses in veterinary medicine, including feline paraneoplastic alopecia, exfoliative dermatitis associated with feline thymoma, nodular dermatofibrosis, feminization syndrome associated with testicular tumors, superficial necrolytic dermatitis and paraneoplastic pemphigus.

The feline paraneoplastic alopecia is a rare condition. The clinical signs have a rapid onset and include ventrally distributed alopecia and shiny skin, while histopathological signs include follicle telogenization and miniaturization. The syndrome may be associated with pancreas carcinoma, cholangiocarcinoma, hepatocellular carcinoma and intestinal carcinoma [56,57].

Florizoone [58] reported a case of exfoliative dermatitis associated with thymoma in a rabbit, with skin biopsies sharing similarities with seborrheic dermatitis (absence of sebaceous glands, perifollicular lymphoma, infiltrate at the level of the absent glands, lymphocytic mural folliculitis and interface dermatitis). The necroscopic assay revealed a mass in the anterior mediastinum, with histopathological assays confirmed the diagnosis. In addition, the differential diagnosis for exfoliative dermatoses in rabbits may be based in the similarities with exfoliative dermatitis associated with thymoma in cats.

Erythema multiforme may also be a paraneoplastic disorder associated to thymoma in dogs, similarly to exfoliative dermatitis associated to thymoma in cats. Tepper., *et al.* [59] reported a case of erythema multiforme in a Labrador Retriever initially presenting severe halitosis, mild ptyalism and nasal depigmentation. Six months after the start of the treatment, the dog showed no signs of improvement and was diagnosed with a mediastinal mass consistent with thymoma.

Superficial necrolytic dermatitis is uncommon in dogs and is associated with systemic metabolic disorders. Torres., *et al.* [60] described that, in dogs, the primary areas affected are the foot pads, the mucocutaneous boundary and the nasal plane. Histologically, all cases presented hyperkeratosis, intra and extracellular edema of keratinocytes in the spinal stratum, basal hyperplasia and su-

perficial dermatitis, being common in West Highland White Terriers, Shetland Sheepdogs and Cocker Spaniels, especially in males around 9.6 years-old.

Animals afflicted by glucagonoma, a rare neuroendocrine tumor occurring in the pancreatic islets, also present skin injuries characterized by superficial necrolytic dermatitis affecting the mucocutaneous boundary, the foot pads, the elbows and the abdomen [61,62].

Another clinical manifestation observed is paraneoplastic pemphigus, a severe interface dermatitis which, in humans, is associated mainly with hematopoietic neoplasms and with an exclusive autoantibody profile. In animals, paraneoplastic pemphigus has been described mostly in dogs, but there are reports in cats, such as the one described by Hill., *et al.* [63] in a case of lymphocytic thymoma. The animal presented masses in the thorax and developed myasthenia gravis two weeks after excision. In addition, the patient developed pemphigus vulgaris and erythema multiforme, a combination suggesting SPN.

In humans, Wang.,., *et al.* [64] reported a case in which the noted the antigenic epitopes concentrated mainly in EVPL-N1 and EVPL-L3. The presence of antibodies against EVPL-N3 may be associated with bronchiolitis obliterans and injuries compatible with lichen planus.

The nodular dermatofibrosis, characterized by the development of multiple cutaneous nodules due to collagen, is another PNS that has been reported. Sfrizo., *et al.* [65] reported this syndrome associated with a bilateral renal cystadenoma in a female dog, with clinical alterations preceding a terminal kidney injury.

In a case of liver metastatic hemophagocytic histocytic sarcoma reported by Soares., *et al.* [66], the quantitative polymerase chain reaction (qPCR) assay verified increased expression of the IL-6 gene in the affected organs, suggesting that neoplastic cells are responsible by the clinical manifestations of the disease, which presented an absence of erythrocytes and albumin in the blood, hypoalbuminemia and regenerative anemia, as well as cytokine release.

Therefore, the skin presents a way to diagnose several systemic diseases and alterations suggesting malignancy. Over 50 dermatoses have been correlated with underlying neoplastic processes in human beings and several are correlated with specific neoplasms, representing an important auxiliary diagnostic tool and clinical marker [64].

Paraneoplastic Syndromes Associated with the Kidneys

Cancer patients may develop complications in the kidneys, such as glomerular diseases associated with stem-cell transplantation and glomerular diseases caused by paraneoplastic processes [67]. Renal paraneoplastic syndromes are a group of diseases indirectly compromised tubular and glomerular function, leading to electrolytic imbalance, secretion of hormones by de tumor or deposition of antigen-antibody complexed in the glomeruli [58].

The most common glomerular pathology associated with solid tumors in human patients is the membranous nephropathy. However, further studies about epidemiology and pathology are needed to verify the true prevalence of paraneoplastic glomerulopathies and research physiopathological approaches since the pathogenesis of most types of cancer associated with glomerular injuries is still unknown [69,70].

Although uncommon, the possibility of an underlying malignancy should be considered with all patterns of glomerular injuries since several solid and hematologic malignancies in humans, such as the minimal change disease, non-Hodgkin's lymphoma, membranoproliferative glomerulonephritis and chronic lymphocytic leukemia, have been associated with several glomerular diseases. Treatment aims mainly at the cancer because remission is often accompanied by improvement in the glomerular manifestations, requiring a multidisciplinary approach in monitoring the cancer and the glomerular injury [70].

Cambier and Ronco [71] reported that the physiopathology of a solid tumor (carcinoma) associated with glomerulopathies is still unknown, but a molecular connection is often observed in hematologic neoplasms induced by paraneoplastic glomerulopathies. Paraneoplastic glomerulonephritis is a rare clinical manifestation that often goes unnoticed due to the lack of specific symptoms and clinical signs, in addition to manifesting clinically as a nephrotic syndrome [72,73].

Another etiology attributed to paraneoplasms is the membranoproliferative glomerulonephritis, common in cases of chronic lymphocytic leukemia, which may present itself as a kidney failure, a proteinuria or an immune complex phenomenon [76]. The syndrome is often mistaken for idiopathic glomerulonephritis, which may lead to patients being subjected to inefficient and possibly harmful therapies [72].

Therefore, it is important to recognize the underlying pathogenetic mechanisms in glomerular injuries apparently related to

altered immune responses [72]. Breakthroughs have happened in human medicine regarding our understanding of the physiopathology of paraneoplastic glomerulopathies, shedding light on their mechanisms and enabling improvements in therapies [71].

Nephrogenic diabetes insipidus (NDI) is characterized by the kidney's inability to reach ideal concentrations for urine despite normal of increased levels of antidiuretic hormone [75]. Primary (congenital) NDI is rare both in humans and animals, but the disease may also be secondary (acquired), most commonly occurring in the manifestation of another underlying pathology such as a PNS [76].

Kidney involvement may also be present in cases of lymphoma, which is caused by several distinct mechanisms varying greatly in prevalence and clinical presentation [76]. Falqueto., *et al.* [77] were reported acquired stenosis in the external auditory canal during disease progression in a man afflicted by kidney clear cell carcinoma, which is the first described case of pyoderma gangrenosum with PNS in this type of neoplasm, highlighting the importance of diagnosing the underlying disease.

In addition to the aforementioned syndromes, kidney function may also be affected by hypercalcemia in malignant neoplasms, antidiuretic hormone inappropriate secretion syndrome, tumor lysis syndrome, renin-producing tumors and paraneoplastic glomerulopathies [78].

Neurologic Disorders

Paraneoplastic neurologic disorders are the results an indirect effect of the tumor in the nervous system or muscle without local invasion or metastasis and are frequently associated to antibodies linked to proteins shared by the tumor and the nervous system [79] In most cases, there is a neurologic disorder before the cancer is identified, but neurologic complications may also develop with tumor development [80,81].

Some paraneoplastic neurologic disorders affect a single area or a single type of cell, while others affect several levels in the nerve and may affect any part of the nervous system [80,81]. In humans, the most common neurologic paraneoplastic syndromes include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus myoclonus, sensory neuropathy, chronic intestinal pseudo-obstruction, Lambert-Eaton myasthenic syndrome and dermatomyositis [82].

Rodigheri., *et al.* [83] were reported two cases of Paraneoplastic Neuropathy (PN) associated with canine mastocytoma, with manifestation of neurological signs concurrently with the development of the cutaneous nodules, highlighting the need for further research correlating mastocyte degranulation with paraneoplastic neurological disorders in animals.

The PNs may manifest as focused or diffuse injuries, as observed in the cases reported by these authors. The first patient presented a history of tetraparesia unrelated to trauma, with the neurological examination revealing preserved deep nociception, hyporeflexia and hypotonia in the thoracic and pelvic limbs, in addition to a cutaneous nodule in the inguinal region.

The second patient, on the other hand, presented a history of apathy, hyporexia, lack of coordination and head tilting with a cutaneous nodule located in the lateral region of the thorax. The neurological examination revealed vestibular syndrome characterized by head tilt and horizontal nystagmus.

Thymomas may be associated with several PNSs, including myasthenia gravis [79]. Robat., *et al.* [84] were reported that 17% of the 114 dogs included in their study presented signs of myasthenia gravis and that the diagnosis was confirmed in 11.21%. The clinical signs were usually unspecific, and most were associated with the respiratory tract or attributable to the presence of paraneoplastic myasthenia gravis.

Gozzard., *et al.* [79] were talked about paraneoplastic neurological disorders (PND) in a case of small cell lung carcinoma, reporting a high incidence of PND. In addition, tests with antibodies SOX2, HuD and VGCC may aid in the identification of small cell lung carcinoma. In humans, the type and frequency of the underlying tumor varies depending on the antibody and its detection is expanded to include antibodies against neuronal surface and synaptic receptor antigens which are excellent predictive markers for a better response to immunotherapy despite not confirming the origin of the PNS [85].

In humans, there are reports of paraneoplastic subacute cerebellar degeneration associated with ovarian tumor, secondary paraneoplastic necrotizing myopathy and tubo-ovarian adenocarcinoma, as well as paraneoplastic disorders in the peripheral nervous system, including motor neurons, sensory ganglia, nervous roots and cranial plexus [86-88].

Mixed Syndromes

Hypertrophic Osteopathy (HO) is an uncommon disease that has been describe in dogs [89-91] and other species, including equines [92,93]. Human beings may also be afflicted by the disease,

[94] which is caused carcinogenic process of other diseases and characterized by general periosteal proliferation affecting primarily the long bones [95,96].

In dogs, the HO is frequently diagnosed as a PNS, most frequently in cases of primary or metastatic pulmonary neoplasms. The syndrome is secondary to a tumor mass in the thorax or abdomen or to a cardiovascular disease. It is characterized by chronic bone neoformation resulting in a significant thickening and deformity in the thoracic and pelvic limbs [97-99]. The syndrome has also been described associated with kidney (transition cell carcinoma) or vesicle tumors (undifferentiated sarcoma, rhabdomyosarcoma), [94] as well as other neoplastic processes including abscesses, granulomas, parasites, pneumonia, pulmonary atelectasis, pulmonary diseases, cardiac diseases, tuberculosis, dirofilariasis and spirocercosis [95,100-104].

In cats, HP is associated with pulmonary adenocarcinoma, renal papillary adenoma, thymoma and bronchogenic carcinoma [102,103]. The pathogeny is still not fully known, and the primary finding is increased peripheral blood flow in the distal part of the limbs together with growth of the vascular connective tissue and subsequent mineralization [105-107]. The proposed hypotheses include the release of toxic molecules by the neoplasms in the bloodstream. These molecules increase blood flow, which stimulates the development of anastomosis arteriovenosa and compromises microcirculation [106,108].

Another hypothesis is that humoral vasoactive substances or neurological stimulation lead to the increased blood flow in the limbs, which stimulates the excessive production of growth hormone contributing towards HP [109,110]. Most injuries reported are bilateral and symmetric but may also afflict all four limbs [111,112]. The disease mainly afflicts old Boxer dogs, but other large breeds also present higher chances of developing the disease in contrast with smaller breeds.

There have been reports in mixed breed dogs, such as the one described by Hoffmann., *et al.* [111] who presented a case of hypertrophic osteopathy involving the joints and proximal bones of the appendicular skeleton secondary to a mediastinal chondroblastic osteosarcoma. Another report by Bernardi., *et al.* [113] presented the case of a Poodle with bone neoproliferation across the entire limbs, which is compatible with HP. Animals afflicted by the disease presented pain and difficulty to move the thoracic and pelvic limbs during the diagnosis. Signals related to thoracic diseases may also be present, including dyspnea, cough, altered pulmonary sounds and cardiac dislocation.

Imaging diagnosis methods, such as ultrasound, radiography and computed tomography may aid in confirming the diagnosis [91,93,94,113,114]. Histopathology is also an important diagnostic tool [91,115]. In clinical terms, the disease causes increased temperatures in the metaphyseal region of the limbs, swelling, pain, cough, progressive weight loss and cachexia [93,116-118]. Fatigue is also clinically noticeable in cancer patients due to a decrease in the individual's energy levels [119].

Cancer patients also present fevers often because of the decreased appetite, leading to malaise [117]. The physiopathological mechanisms result in the production of pyrogenic cytokines by the tumor and/or the host's immune system. The pathogenesis of paraneoplastic fever is caused primarily by excessive cytokine synthesis, including IL-1, IL-6, TNF-α and interferons, as well as fever-inducing prostaglandins [100,118]. The treatment is conducted with non-steroid antipyretic or anti-inflammatory agents [100,119].

When possible, the treatment for the tumors include surgical procedures. In case where that is impossible, oral prednisolone (1-2 mg/kg) may be used as an alternative [101,103]. Excision of the intercostal nerves, unilateral vagotomy and bilateral cervical vagotomy have also been reported [120,121]. The administration of bisphosphonates is a new procedure in veterinary medicine for cases of hypertrophic osteopathy, which may represent a new therapeutic avenue for cats and dogs [122].

Conclusion

The number of paraneoplastic disorders reported in human cancer patients is larger than the one reported in animals, highlighting that more these diseases may be underdiagnosed in the latter. In addition, the real incidence of these alterations is unknown in veterinary medicine since studies include more reports in small animals.

Therefore, understanding the types of paraneoplastic syndromes and their causes is primordial to an early diagnosis and to the selection of an adequate therapy, avoiding unnecessary procedures and leading to better prognoses. For such an end, more diagnostic tests need to be conducted and further and more reliable studies with a considerable number of patients are warranted.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Volume 3 Issue 2 February 2019