



Objective

This final degree project is intended to be a compilation of the current scientific literature revolving paraneoplastic syndromes (PNS) in canine medicine, their known incidences, associated neoplasms and proposed functioning mechanism. It also intends to reflect the perception of PNS by Spanish veterinarians in their clinical cases, using it as a base to compare both literature and professionals' perception.

Introduction

- A PNS is a neoplasm-associated alteration in bodily structure or function that occurs distant to the tumor.
- They are a relatively new area of study revolving cancer.
- Pathogenesis varies among syndromes but several humoral and immune mediators are implicated, as well as the tumors' acquired ability to secrete a variety of bioactive substances.
- Signs of the PNS may be what actually prompt veterinary evaluation in the first place.
- They have been described in many species and affecting a large variety of organs and tissues and they have been proved to have a very important role in early recognition of the disease as well as in its course, its treatment and its prognosis.
- Table 1 summarizes the known data regarding PNS and their associated tumors, incidence and main mechanisms.
- In nephrotic syndrome, retinopathies, optic neuropathies and dermatomyositis; incidence, mechanisms and associated tumors are unknown.

Table 1

Syndrome	Main tumors	Incidence	Most probable mechanism
Cancer cachexia	Multiple tumors	Frequent	Hormonal or cytokine-mediated
Gastrointestinal ulceration	MCT, gastrinoma	Up to 75% of dogs with MCT	Excess histamine production
Protein-losing enteropathy	Gastrointestinal neoplasms	Rare	Mucosal erosion, ulceration or lymphatic obstruction
Hypercalcemia of malignancy	Lymphoma and others	Frequent	Ectopic production of PTH
Hypoglycemia	Insulinoma and others	Frequent	Hyperinsulinemia
SIADH	Hypothalamic tumor	Rare	Ectopic/excessive production ADH/ADH-like molecule
Ectopic Cushing syndrome	Primary lung tumors	Rare	Ectopic ACTH secretion
Hyperglycemia	Pituitary tumors, adrenocortical tumors, glucagonoma	Rare	Production of several hormones by the tumor or resistance to insulin
Hyperglobulinemia	Multiple myeloma, plasmacitoma, lymphoma, leukemia	Frequent	Excessive production of immunoglobulins
Anemia	Multiple tumors	Frequent	Depends on the kind of anemia
Erythrocytosis	Kidney, lung or liver, lymphoma and others	Rare	Primary erythropoietin excessive production or secondary to renal hypoxia
Leukocytosis	Lymphoma, fibrosarcoma, carcinomas	Rare	Production of colony-stimulating factor or cytokines by the tumor
Thrombocytopenia	Spleen tumors, lymphoma, leukemia	30% of solid tumors and 58% of lymphomas	Anti-platelet antibodies and cross-reactivity between platelet antigens and tumor antigens
DIC	Hemangiosarcoma and others	Frequent	Coagulation-activating substances produced by the tumor
Cutaneous flushing	Pheochromocytoma, carcinoids, MCT	Unknown	Unknown
Nodular dermatofibrosis	Cystadenocarcinoma, cystadenoma	Rare, only in German Shepherd	Autosomal dominant inheritance
Superficial necrolytic dermatitis	Glucagonoma, glucagon-producing pancreatic tumors	Seven reported cases	Hypoaminoacidemia secondary to chronic glucagon elevation
Pemphigus	Mediastinal lymphoma and splenic sarcoma	Two reported cases	Autoimmune process initiated by lymphoproliferative disorder
Diabetes insipidus	Leiomyosarcoma	Rare	Unknown
Glomerulonephritis	Polycythemia vera, leukemia and others	Unknown	Immune complex or amyloid deposition and hypercalcemia
Myasthenia gravis	Thymoma	Up to 47%	Autoantibodies bound to acetylcholine receptors
Peripheral neuropathies	Insulinoma, leukemia, lymphoma and others	Unknown	Insulin excess causing sustained hypoglycemia
Uveitis	Renal lymphoma	One possible case	Immune-mediated
Hypertrophic osteopathy	Lung tumors, osteosarcoma and others	Unknown	Vasoactive substances secreted by the tumor or neurological stimulation
Fever	Lymphoma and others	Unknown	Production of endogenous pyrogens (IL-1, IL-6, TNF- α)

MCT, most cell tumor; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; ADH, anti-diuretic hormone; ACTH, adrenocorticotrophic hormone; DIC, disseminated intravascular coagulation.

Methods

A survey was composed regarding PNS and their presence in the professional activity of Spanish veterinarian doctors. It was answered by 42 veterinarians.

The survey is formed by two main parts:

- Signaling PNS they had encountered from a basic classification (gastrointestinal, endocrine, hematological, dermatological, renal, neurological, ophthalmological and musculoskeletal).
- Estimate frequencies about concrete syndromes depending on the previous answer.

The frequency was estimated in a scale of 1 to 5 (1=never; 2=very rarely; 3=few times; 4=every now and then; 5=frequently).

Results and discussion

Some discrepancies have been found when compared certain results with the current literature.

Regarding protein-losing enteropathy and leukocytosis, the incidence is higher when asked to veterinarians than that described in literature. The exact opposite happens with hypoglycemia.

Information in literature is scant regarding cutaneous flushing, glomerulonephritis, dermatomyositis, retinopathies, optic neuropathies and nephrotic syndrome, so no comparison was possible.

The percentage of veterinarians who say to have encountered uveitis, diencephalic syndrome, pemphigus and superficial necrolytic dermatitis as a PNS is very shocking when compared to the literature, as little few cases have been described whereas respondents claim to have found them quite often.

The rest of the results are not far from what expected when comparing them the literature.

The results of the survey are summarized in Table 2. The middle column refers to what percentage of the 42 participants ever encountered a particular PNS whereas the right column reflects the frequency in which the participants that encountered this particular syndrome believe they stand in front of it amongst their oncological cases.

Table 2

Syndrome	Percentage of vets who encountered it	Perception of incidence	Syndrome	Percentage of vets who encountered it	Perception of incidence
Cancer cachexia	71%	Frequent	Glomerulonephritis	38%	Rare
Protein-losing enteropathy	69%	Frequent	Nephrotic syndrome	38%	Rare
Gastrointestinal ulceration	67%	Frequent	Myasthenia gravis	33%	Rare
Hypercalcemia of malignancy	57%	Frequent	Hyperglycemia	31%	Rare
Anemia	57%	Frequent	Nodular dermatofibrosis	26%	Rare
Leukocytosis	57%	Frequent	Diabetes insipidus	26%	Rare
Thrombocytopenia	57%	Frequent	Superficial necrolytic dermatitis	24%	Rare
Coagulopathies	52%	Frequent	Diencephalic syndrome	24%	Rare
Hyperglobulinemia	50%	Frequent	Retinopathies	24%	Rare
Cutaneous flushing	50%	Frequent	Ectopic Cushing syndrome	21%	Rare
Hypoglycemia	57%	Rare	Pemphigus	21%	Rare
Peripheral neuropathies	50%	Rare	Optic neuropathies	21%	Rare
Erythrocytosis	48%	Rare	SIADH	17%	Rare
Uveitis	48%	Rare	Dermatomyositis	10%	Rare

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Conclusions

The disparity between information obtained from the survey and that obtained from literature may be explained by:

- Misinformation: clinicians will rarely identify signs or symptoms they have never heard of.
- Not all existing cases are published.
- Disinterest of respondents for somebody else's work may result in erroneous or invented answers.
- Misunderstanding of the survey could lead to unintended error. Human element must always be taken into account.

More studies are needed in order to achieve better knowledge in that field.