Proceedings of the
World Small Animal Veterinary Association
Mexico City, Mexico – 2005

Hosted by:

Reprinted in the IVIS website with the permission of the WSAVA
INTRODUCTION

Autoimmune diseases may be defined, in a simple way, as the disorders in which a patient’s immune system directs its response against the patient itself, in an erroneous and unusual manner. Such events may be mediated through autoantibodies whose attack is directed against particular cutaneous protein extracts (pemphigus complex, pemphigoid), of autoantibodies that, when bound to antigens, release antigen-antibody complexes that deposit in the basement membrane zone (lupus erythematosus), or through the release of deleterious substances by lymphocytes (erythema multiforme, toxic epidermal necrolysis – Lyell’s syndrome). All of these dermatoses have been evidenced in small animals, as were other dermatoses less frequently observed, such as vitiligo, uveodermatologyc syndrome, epidermolysis bullosa acquisita, vasculitides, alopecia areata and the pseudopelade. Pemphigus complex and lupus erythematosus constitute the two most frequently diagnosed autoimmune disorders around the world. Today, the state-of-the-art veterinary dermatology favors the diagnosis as well as the therapeutic control of such diseases.

INCIDENCE

Among all dermatoses examined at university small animal practices, it is estimated that 0.6 to 1.4% of North American dogs have some form of autoimmune disease. Meanwhile, in Brazil, such disorders are observed in 0.3 to 1.1% of the dogs. It is evident, though, that the incidence of autoimmune dermatoses is greater than these numbers suggest, both in Brazil and elsewhere.

At the College of Veterinary Medicine of the University of São Paulo, Brazil in the period ranging from 1986 to 1998, incidence of autoimmune dermatoses has been rated in decreasing order as: lupus erythematosus (51.5%), pemphigus complex (26.5%), uveodermatologyc syndrome (19.1%) and other autoimmune dermatoses (2.9%).

PSPHIGUS COMPLEX

This complex, whose existence has been noted throughout the millennia, comprises the pemphigus foliaceus (PF/Cazenave Disease), pemphigus erythematosus (PE/ Senear-Usher Disease) and pemphigus vulgaris (PV) among the most frequent forms. Other forms that account for smaller incidence embody the panepidermal pustular pemphigus, drug-induced pemphigus and paraneoplasic pemphigus. For a long time, the pemphigus foliaceus and erythematous were classified as “essential” or “superficial” forms, in contrast to the pemphigus vulgaris which was denominated “deep pemphigus.”

In the mid-XX century, an endemic form of pemphigus was frequently diagnosed in South American countries including Brazil, whose form was well characterized in human patients. Such form of the disease received the name of “endemic pemphigus,” “Brazilian pemphigus,” “South American pemphigus” or yet, “fogo selvagem” (FS). Today, this less frequently diagnosed form of the disease bears familial occurrence, committing young adults and children who live near rivers in rural areas. Endemic pemphigus is still followed and researched in indian populations in central Brazil. Besides the evident genetic predisposition, it is thought that additional factors may be involved in the pathogenesis of the disease, such as exposure to black flies. Sporadic cases of FS involving human patients have been documented in Paraguay, Peru, Bolivia, Colombia and Argentina. Cases involving animals were never documented.

The different types of pemphigus have a common pathomechanism. They are caused by autoantibodies (IgG and, at times, IgA or IgM) directed against membrane proteins (desmogleins of the cadherin group of adhesion molecules). The target antigen varies according to the type of pemphigus. Hence, with pemphigus foliaceus the attack is directed against desmossomal desmoglein I (160KDa) whilst in pemphigus vulgaris, the target antigen is desmoglein III (130KDa). This mechanism yields acantholysis,
which is the loss of adhesion among cells of the Malpighi layer. It is believed that the rupture of the intercellular adhesion would result from the internalization of the pemphigus antibody and fusion of this antibody with intracellular lysosomes, activating and releasing proteolytic enzymes (urokinase plasminogen activator-uPA) which would convert extracellular plasminogen to plasmin which would in turn hydrolyze the adhesion molecules 13, 14, 20, 21.

Little is known about the mechanism through which autoantibodies (IgG 1 or IgG 4) are produced. Would it result from change in immune regulation or through an anomalous antigenic stimulus? Other than the genetic predisposition of certain breeds (Chow Chow, Labrador, Akita) there would be additional factors to be considered, such as infectious agents, environmental components (sun, tannins, humidity, heat), drugs (sulfa, griseofulvin, ampicillin), and chronic skin disorders (neoplasias, flea bite hypersensitivity).

Recently, it has been emphasized that serum levels of antikeratinocyte autoantibodies hold close relation with the activity observed in patients with pemphigus foliaceus and that such antibodies, isolated from pemphigous dogs, would cause acantholysis in neonate mice 18, 19.

A scarce number of South American casuistic studies show that, within the pemphigus complex, pemphigus foliaceus is the most frequent condition followed by pemphigus vulgaris 10.

The first reported cases of canine pemphigus foliaceus in South America were documented in 1987 and 1995 in Argentina and Brazil, respectively 8, 15. It has been described in South American cats only in Brazil 14. A single case of canine pemphigus vulgaris was described in 1989 12. In Brazil, there have been two reported cases of pemphigus erythematous 17.

According to casuistic studies at the Dermatology Service of the College of Veterinary Medicine of the University of São Paulo (USP), over a 15-year period, a total of 30 cases of canine PF and one case of feline PF were diagnosed 3. Among Brazilian dogs, it is more frequent in pure-bred animals (60%), more commonly in Cocker spaniels (28 %) and German shepherds (17%), and females (56.7%), with a mean age of 61 months and range of four to nine years (66.5%). In North American and European countries, it has been commonly described in Collies, Akitas, Dobermans, Setters, Newfoundlands, Dachshunds, Chow Chows and Siberian huskies 3,8, 18, 23, 24, 26.

The pemphigus foliaceus and pemphigus erythematous are characterized by the abrupt onset of a pustular dermatitis, presenting ephemeral, irregular, sometimes follicular pustules whose diameter ranges from 1 to 10 mm. As these pustules rupture, they originate epidermal collarettes, erosions and honey-colored crusts. Lesions are generally found in the face and ears, later involving footpads (villous hyperkeratosis) and the inguinal region. They may disseminate or generalize in one to three years (27%). About 60% of the dogs present rapid generalization within a six-month period. Manifestation through sole footpad-lesions is uncommon. In cats, other than face and pinnae, there is frequent involvement of nipples and nailbed (onychodystrophy, onychorrhexis, onychogryphosis). It is not uncommon for animals with pemphigus foliaceus to suffer concomitantly from dermatophytosis and scabies, even before therapy with corticosteroids 3,13,15.

Dermatologic examination may reveal the presence of the Nikolsky sign. Pruritus is present in 70% of the cases 3. Fever, pain, prostration, lameness, generalized lymphadenopathy and anorexia may be present at times 22. One is unable to convey human symptoms of Fogo Selvagem (burning sensation, sensation of intense heat, increased sensitivity to cold) to animals. Nonetheless, one may sense the “rat’s nest” stench in generalized pemphigus foliaceus.

Pemphigus erythematous presents the same elementary cutaneous lesion pattern, though it is usually circumcresced to face and pinnae. Nowadays, human dermatologists 21 consider PE as the forma frustra (“frustrated” form) of pemphigus foliaceus and, exceptionally, of pemphigus vulgaris. The form called Seener-Usher syndrome encompasses cases of pemphigus, lupus erythematous and seborrheic dermatitis.

Pemphigus vulgaris was the first disease of the pemphigus complex ever to be described in veterinary medicine, 29 years ago, by Stannard. In Brazil, the first recorded case dates from 1989 12. In the United States and in Brazil, it represents about 44% of all pemphigus cases 1, 13. Its primary lesions consist of suprabasillar vesicles or bullae, which are relatively long-lasting. Oral lesions such as glossitis, stomatitis and gingivitis seem to be present in 50 to 60% of the cases. 90% of these dogs present such lesions at the time of the diagnosis. This disorder is more common in pure-bred dogs (Brazil: 73%; USA: 85%) such as Poodles, Schnauzers, Cockers and German shepherds 1, 13. Seborrhea and halitosis may be prominent. It may evolve to mucocutaneous junctions, as well as to axillae, groin and claw-bed 18, 22. The case is always deemed severe, leading to intense debilitation given the dysphagia, prostration, hyperthermia and intense pain, often leading to death 22.

The diagnosis for PF, PE and PV is based on animal identification (race, sex, age), history, physical
and otologic and dermatologic examination and laboratory testing (cytological examination: acanthocytes or Tzanck cells in the case of PF and PE; histopathologic findings, immunofluorescence and immunohistochemical testing). Out of these, perhaps the most viable exam is the classical histopathology of biopsied lesions, preferably preserving the clefting point via excision biopsy. Histologically, the pemphigus complex is characterized by intraepidermal acantholysis (intergranular or subcorneal), intraepidermal clefting, vesicle or pustule formation and acantholytic keratinocytes. Within these vesicles lie cells from the stratum granulosum attached to the overlying stratum corneum. Interface lichenoid dermatitis is present with pemphigus erythematosus. Cases of pemphigus vulgaris reveal suprabasilar acantholysis.

Despite significant improvement in immunopathological examinations (direct and indirect immunofluorescence) in veterinary medicine, clinical findings and classical histopathology should always be taken into account.

The differential diagnosis of pemphigus foliaceus comprises pemphigus erythematosus, bullous impetigo, subcorneal pustular dermatosis, necrolytic migratory erythema and lapus erythematous. Pemphigus erythematosus should be differentiated from pemphigus foliaceus, discoid lupus erythematous, uveodermatologic syndrome and mycosis fungoides. Finally, pemphigus vulgaris may be confounded with drug-induced eruptions and with bullous pemphigoid.

Treatment is dependent on the type of pemphigus. Pemphigus erythematous may be treated topically. Severe cases of pemphigus erythematosus and cases of pemphigus foliaceus and pemphigus vulgaris should be treated with corticosteroids, preferably prednisone or prednisolone where the latter should be used mainly in pemphigous felines. Alternatively, one may employ triamcinolone (difficult to obtain in Brazil and USA) and dexamethasone. Dosage should always be selected as to induce immunosuppression (prednisolone/prednisone: 2 - 8 mg/kg SID; triamcinolone 0.2 – 0.8 mg/Kg BID; dexamethasone 0.1 – 0.2 mg/Kg BID). Depending on the consulted author, up to 80% of pemphigus cases are refractory do corticosteroids. In Brazil, prednisolone (2mg/Kg SID) has proven to be effective in 83% of the patients. Alternatively, one may employ an association of prednisolone-azathioprine in dogs or prednisolone-chlorambucil in cats. Chrysotherapy or gold-therapy (aurothioglucose, auranofin) is of little effect and frequently generates serious side-effects. Recently, therapy with mophetil micofenolate and cyclosporine “per os” has been instituted, however it has yielded frustrating results at a high costs.

BIBLIOGRAPHY

5. FONDATI, A. Personal communication - Informação Pessoal. 2001.

Contact with the author: larsderm@usp.br

Pemphigus – term derived from the Greek (“pemphix,” “pomphos,” “pompholix”), cited in the Old Testament (“abab’oth”) and by Hippocrates (“pemphigoides pyretoi”), was latinized by François B. Sauvage in 1874.

Faculdade de Medicina Veterinária e Zootecnia da Universidade de São Paulo (Brazil)