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# PRURITUS AND LEISHMANIASIS: HOW DO I MANAGE IT?

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## INTRODUCTION

Skin problems are very common in everyday veterinary practice, accounting for around 22% of all consultations in dogs.[1] Almost 40% of dermatological visits are due to the presence of pruritus. A very common cause of pruritus in dogs is allergic dermatosis, with atopic dermatitis being the most frequently encountered form. This is a truly complex, immune-mediated and multifactorial condition, resulting from an inappropriate immune response to common environmental allergens, primary and secondary alterations of the skin barrier, and imbalances in the physiological microbiota of the skin. ([2,3])

The clinical signs associated with atopic dermatitis usually appear during the early stages of an animal's life, but as it is a recurrent and chronic clinical condition, affected patients live with it for years. This means that comorbidities may arise that complicate the clinical picture or force us to modify and adapt our therapeutic decisions for the management of atopic dermatitis and pruritus.

Considering that we work in an endemic area, leishmaniasis is one of these comorbidities, and we must keep it in mind at all times. Although it is considered a systemic disease, it is very common for affected dogs to present with skin lesions, which are the reason for consultation in more than half of cases and may be the only detectable clinical sign in up to 89% of them.([4-6])

Dermatologically, leishmaniasis is highly pleomorphic and can present with a variety of symptoms, some more common and typical than others. Among these, the most frequent are exfoliative, erosive-ulcerative and nodular dermatoses, which are not pathognomonic of the disease and may also be compatible with many other dermatoses.[4-6]

Although it is true that pruritus is not a clinical sign that frequently accompanies leishmaniasis, the changes that occur in the skin can lead to the appearance of secondary infections that cause itching. Likewise, if the clinical history and progression of the dermatological condition are unclear, some lesions related to leishmaniasis could be confused with self-inflicted lesions secondary to intense pruritus in allergic animals, such as some erosive-ulcerative lesions, for example. And if all this were not enough, an allergic dog may develop leishmaniasis during its lifetime (due to living in an endemic area or repeated use of immunosuppressive drugs to control pruritus), which could lead to the appearance of new lesions that we could mistakenly attribute to the natural progression of the underlying allergic dermatosis.

Given all this, it seems essential to bear leishmaniasis in mind in all patients with dermatological problems, especially if they need to take drugs to control pruritus, some of which have immunosuppressive properties.

## HOW CAN I MAKE THE DIAGNOSIS?

Dermatology is a highly visual discipline, and in most cases the differential diagnosis is based on the macroscopic appearance of the lesions (clinical pattern). In fact, atopic dermatitis is diagnosed clinically, as there is no specific diagnostic test for this purpose. Thus, it is highly likely that a young dog is atopic if, after ruling out infections and ectoparasites, it presents pruritus that mainly affects the ventral regions, face, distal region of the limbs and/ r inner surface of the auricles. In addition, these dogs usually respond excellently to drugs such as glucocorticoids or oclacitinib.([7])

The diagnosis of leishmaniasis is somewhat more complex, as the different lesions we observe are the result of an immune response and a different pathophysiology; furthermore, it can occur in animals of almost any age (which can complicate the clinical suspicion). Thus, we will not use the same diagnostic methods in a dog in which we see an ulcerative lesion that we suspect is due to vasculopathy secondary to the

deposition of immune complexes, as in a dog with sebaceous adenitis due to leishmaniasis and generalised desquamation. The diagnostic method chosen will depend in each case on the type of lesion and the clinical history.([4,6,8-10])

Below is a list of the most common lesions in both pathologies, some of which can be confused.

**Classic dermatological lesions in allergic dogs**

Pruritus
Erythema
Lichenification
Scaling
Erosions/excoriations
Alopecia/hypotrichosis (due to scratching or secondary folliculitis)
Pustular dermatitis if there are secondary infections
Inflammatory plaque-nodular lesions due to chronic inflammation/deep pyoderma
Interdigital nodules
Otitis externa
Generalised lymphadenopathy due to skin inflammation

**Dermatological lesions in dogs with leishmaniasis**

Exfoliative dermatosis
Ulcerative dermatosis
- On bony prominences
- In areas of chronic trauma
- On the nose
- On extremities of the body (ear tips, tail)
- At mucocutaneous junctions

Papular or nodular dermatosis
Multifocal alopecia
Pustular dermatitis
Onychogryphosis
Nasodigital hyperkeratosis

In all dogs with skin lesions compatible with leishmaniasis, it is essential to perform a cytology, as this can clearly help us in the diagnostic approach. However, this will not always be the case, and it will depend greatly on the type of lesion, as we will see during the talk. Likewise, the concomitant use of systemic diagnostic techniques will be essential, as they will be very important for the initial diagnosis and for monitoring treatment.

**WHY DOES THE EXPRESSION OF LEISHMANIOSIS VARY SO MUCH FROM ONE PATIENT TO ANOTHER?**

There are various types of adaptive immune system responses in dogs infected with *Leishmania* spp. These responses depend largely on how the innate immune system manages the infection during the first 24–48 hours. Thus, cells such as neutrophils, macrophages, and dendritic cells will be responsible for recognising the parasite (via *Toll-like* receptor *(*TLR) membrane receptors). After this initial contact, and depending on the receptors involved, they will produce different types of cytokines that will determine the predominant adaptive immune response by T helper (Th) lymphocy , varying between Th1 and Th2. The balance between these two responses will be key to managing the disease. ([11-13])

The Th1 (cellular) response has traditionally been considered "protective". In this response, Th1 lymphocytes release IFN-gamma, TNF-alpha and IL2. This leads to a large activation of macrophages, which are the cells that will control the parasite most effectively (decreasing the parasite load and resulting in low antibody levels in serology). On the other hand, if the Th2 (humoral) response predominates, a greater amount of antibodies is produced; in addition, there is a release of cytokines, such as IL4, IL10 and TGF-beta, which antagonise the effects of IFN, decreasing the cellular response and control of the parasite([14-17]).

There are genetic factors that determine susceptibility or resistance to *Leishmania infantum*, determining the type of immune response: resistant breeds such as the Ibizan Hound tend to develop a protective Th1 response, while susceptible breeds such as the Boxer or German Shepherd tend to have an ineffective Th2 response, leading to the development of the disease[14] .

Therefore, as a concept, we are interested in preserving and/or enhancing the cellular response (Th1) in all infected dogs. As a general rule, the more efficient the Th1 response, the better the control of the infectious disease.

**POSITIVE FOR LEISHMANIOSIS. DO I STOP HERE?**

Leishmaniasis, understood as a systemic disease, goes far beyond detecting the presence of disease. Completing the diagnostic protocol is necessary to classify the patient with leishmaniasis and associated comorbidities, as well as to individualise treatment and follow-up.

Despite often being the test of choice, a positive serological quantification of antibodies against *Leishmania* spp. should not always be interpreted as active disease, especially in an endemic area. In addition to general tests, there are alternative methods in dermatology such as cytology, histopathology, PCR or immunohistochemistry of the lesion, which can confirm the role of the microorganism in the patient's clinical situation. However, it should be noted that the choice of diagnostic tests will depend on the type of lesion and, in turn, on the mechanism that causes it. In the presentation, we will discuss what type of test to perform in each case.

In cases where systemic leishmaniasis is confirmed, it is necessary to complete the patient's profile with a complete haematological and biochemical analysis, a proteinogram, a complete urine analysis and blood pressure measurement. It should be noted that the presentation of dermatological leishmaniasis does not indicate that it is limited to the skin, so monitoring of other systemic alterations remains essential. All of this facilitates the choice and adjustment of treatment, especially in patients with other diseases.

In patients who present with both leishmaniasis and atopic dermatitis, management becomes particularly delicate, as both processes involve alterations of the immune system, but with different mechanisms. Therefore, any therapeutic intervention that modifies immunity may compromise the control of *Leishmania infantum* and favour the progression of systemic disease. Maintaining an adequate immune balance in these patients is crucial, as is achieving balanced control of both pathologies.

**SO, HOW DO I CHOOSE THE BEST ANTI-ITCHING AGENT IN ALLERGIC PATIENTS IN WHOM WE HAVE DIAGNOSED LEISHMANIASIS?**

It is worth remembering that the management of atopic dermatitis must be multimodal, as we are dealing with a multifactorial pathology. Therefore, improving the functionality of the skin barrier and avoiding imbalances in the microbiome should also be part of our therapeutic plan. Even so, many patients will need antipruritic drugs, which we will have to adapt if there are comorbidities such as leishmaniasis, in which we do not want to suppress or clearly modify the patient's immune response.

***As a rule of thumb, the ideal drug for controlling pruritus in an allergic dog that also develops leishmaniasis is one that is safe in the long term, has a moderate impact on the immune system and few therapeutic targets, but at the same time has high antipruritic and anti-inflammatory power.***

Thus, it seems appropriate to think that our cascade of therapeutic decisions should lead us to recommend lokivetmab or oclacitinib as first choices, depending on the degree of inflammation. Likewise, other strategies that allow for drug savings in these patients, such as improving the skin barrier or stabilising the microbiota, will be ideal.

In cases where it is necessary to use drugs with greater immunosuppressive potential, more thorough monitoring of the patient will be key to controlling a possible exacerbation of clinical signs or worsening of

leishmaniasis. We must not forget that some dermatological clinical conditions caused directly by leishmaniasis require the use of glucocorticoids (such as cases of vasculitis).

**Table. Antipruritic drugs with adequate scientific evidence currently available for the control of allergic pruritus in dogs**

| Fármaco | Utilidad para el control de cuadro agudo | Utilidad para el control a largo plazo | Ventajas | Desventajas |
|---|---|---|---|---|
| **Oclacitinib** | SI | SI | Inicio de acción rápido<br>Antiprurítico y antiinflamatorio<br>Pocos efectos adversos | No registrado en perros de menos de 1 año<br>Precaución en perros con neoplasias |
| **Lokivetmab** | SI | SI | Inicio de acción rápido<br>Seguro con otros fármacos<br>Seguro con comorbilidades<br>Se puede usar a cualquier edad | Poco efecto antiinflamatorio |
| **Corticosteroides** | SI | SI* | Inicio de acción rápido<br>Antiprurítico y antiinflamatorio | Múltiples efectos adversos a largo plazo |
| **Ciclosporina** | NO | SI | Permite balancear dosis a largo plazo | Inicio de acción lento<br>Efectos adversos potenciales |

## PATIENT FOLLOW-UP WHAT IF IT RECURS?

It is important to remember that, in atopic dogs, the appearance of new lesions or lack of response to treatment does not always correspond to an outbreak of the disease. In endemic areas such as Spain, leishmaniasis can act as a concomitant disease, appear as a secondary comorbidity to prolonged use of immunosuppressive drugs, or present independently in an allergic patient, making it essential to evaluate each episode individually.

Similarly, in dogs that are seropositive for *Leishmania* spp., the presence of skin lesions does not always indicate a reactivation of the disease. It is important to perform a thorough dermatological examination and assess the type of lesion, which may also lead us to consider other diagnoses or comorbidities, as we will see in the clinical cases during the talks.

A structured follow-up protocol will provide us with a comprehensive view of the patient, allowing us to differentiate between the disease and comorbidity, as well as to adapt the medical treatment to the animal's needs, avoiding complications or recurrences.

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