**DERMATITIS LINKED WITH HELMINTHIC INFECTIONS**

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**Clinical aspects of dermatitis associated with *Dirofilaria repens* in pets**

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**INTRODUCTION**

1- This lecture is focused on clinical signs of dermatitis associated with *Dirofilaria repens* infection in pets.

2- I will not use the term ‘infestation’, but ‘infection’, because it seems more appropriate for a parasite that affects the internal body’s tissues and the blood.

3- The speech is centered on dermatological signs due to *D. repens*. However, in order to fully understand its pathogenicity, we also need to examine biological cycle, vectors, zoonotic aspects, diagnostic tests, therapies and preventive medication.

4- Moreover, since I hope too share with you an interest in history of medicine I will try to elucidate briefly the development of scientific knowledge on this parasite during the last 5 centuries.

5- Probably one of the best kept secrets in veterinary dermatology, subcutaneous dirofilariasis is a parasitic disease endemic in Southern and Eastern Europe, and many parts of Africa and Asia,
caused by *Dirofilaria* (*Nochtiella*) *repens* (Order: Filaroidea; Family: Onchocercidae), a parasite of the subcutaneous connective tissues of dogs, cats, wild carnivores and humans.

6- Three filarial parasites affect pets in Europe and Asia: *D. immitis*, *Acanthocheilonema reconditum*, and *D. repens*.

7- *Dirofilaria immitis* lives in the heart and large vessels (heartworm), and is occasionally reported in abscess-like lesions in the skin, especially on the legs. These locations are erratic and unusual. Pruritic papulo-nodular dermatitis has been associated with these locations and probably is the result of hypersensitivity to the presence of adults in the skin.

8- Dogs with heartworm-associated dermatitis typically show chronic itching, ulcerated papules, nodules and plaques. Lesions are most commonly found on the head and on the limbs but can be anywhere. With standard heartworm treatment the lesions become non pruritic within 2 weeks and heal completely within 8 weeks.

9- Diagnosis is based upon a positive test for circulating heartworm antigens and a Knott’s test revealing *immitis* microfilariae which are shorter (220-230 microns) and thinner (5-6 microns) compared to *repens* microfilariae, with a cephalic end larger than the rest of the body and a tail very thin.

10- A second species, *Acanthocheilonema* (*Dipetalonema*) *reconditum*, affects dogs from Europe, America and Asia with no evidence of clinical signs. However, Hargis and colleagues reported (Veterinary Dermatology, 10:95, 1999) a filariasis, apparently due to an *Acanthocheilonema*-like parasite, in 10 dogs from the western United States showing pruritic papules and plaques with alopecia, scarring, erythema, ulceration and crusting. The head, neck and shoulders were most commonly affected. Three consecutive ivermectin injections cleared the infection.

11- *Acanthocheilonema reconditum* microfilariae are 4-5 microns in width only, much thinner than those of *immitis* or *repens*, and their tail is frequently hook-shaped.

**BIOLOGY OF DIROFILARIA REPENS**

12- The most important agent of subcutaneous dirofilariasis in pets remain *Dirofilaria* (*Nochtiella*) *repens*.

13- Adult parasites, ranging from 1 to 100, are located in the subcutaneous tissues and intra-muscular interstices, and cannot usually be seen or detected, due to their location and migration in
the internal parts of the body host, occasionally producing a subcutaneous nodule or showing up in sub-conjuctival sites (eye).

14- Male measures 5-7 centimeters in length and are 370-450 microns in width. Female are bigger: 10-17 centimeters in length and 460-650 microns in width.

15- At microscopic examination, cuticular longitudinal ridges are present over the entire length of the adult body, except for the two ends, and this constitutes the main difference with *Dirofilaria immitis* in which ridges are absent.

16- The cephalic end of the adult shows: mouth, oesophagus, 10 papillae (and the vulva, in females).

17- After mating, ovoviviparous females produce microfilariae, which constitute the L1 larval stage.

18- At microscopy, *repens* microfilariae measure 325-375 microns in length and 6-8 microns in width showing a cephalic space short, roundish and empty, as well as a tail larger than those of *D. immitis* and *Acanthocheilonema reconditum*. They have a typical wide squat aspect and their caudal end is large.

19- Microfilariae circulate in the blood of domestic pets for 5-9 months until they are captured by a mosquito vector during his blood meal.

20- A number of *Anopheles, Aedes and Culex* mosquito species suck the blood of definitive hosts (dogs, cats and wild carnivores) ingesting microfilariae (L1 larval stage), which develop into L2 and infesting L3 larvae in the insect within 10-20 days.

21- In Italy, many suitable vectors for *D. repens* exist, including the Asian Tiger mosquito *Aedes albopictus, Aedes caspius, Aedes vexans, Anopheles maculipennis, Culex modestus* and *Culex pipiens*.

22- The L3 larvae migrate into the mosquito’s head, reach the labium and actively penetrate into the subcutaneous tissues and capillary vessels of the dog during a blood meal.

23- In the final host, L3 larval stages develop into L4 and adults (L5) stages within 7 months, mostly residing in same location in which they penetrated.
DIAGNOSIS
24- Diagnosis is based upon the presence of pruritic skin lesions, the finding of D. repens microfilariae and a negative test for circulating D. immitis antigens.

25- Differentiation is also possible using the phosphatasic acid histochemical technique: the sediment of centrifuged blood is stained with alfa naphtyl ASTR phosphate which evidences two areas of phosphatasic acid activity in brick red colour for D. immitis microfilariae and one area only, at the posterior end, for D. repens.

26- PCR is today available as well.

EPIDEMIOLOGY
27- Endemic areas of canine and feline subcutaneous dirofilariasis have been described in the Mediterranean countries where human cases also have been reported. This is in accord with the notion that geographic distribution of human dirofilariasis follows the distribution of animal dirofilariasis.

28- Dogs, cats and wild carnivores, in fact, are final hosts of D. repens and constitute the only source of accidental infection to humans, in the presence of a competent population of mosquito vectors.

29 - Cats are apparently less susceptible than dogs. Italy is the only European country where repens microfilariae have been found in cats.

30 - In 2000 I examined 11 autochthonous feline cases in the area between Pavia, Alessandria and Casale in Piedmont, northern Italy. By the way this is considered the most endemic area in the world!

31 – I further diagnosed 19 feline cases in Central Italy: 14 from Umbria (Trasimeno lake), 2 from Tuscany (Chiusi lake) and 3 from Marche (Fermo), all associated with pruritic dermatitis, including alopecia, erythema, papulae, crusting and lichenification. The arrow indicate the location of one reported human case.

32 - These findings were recently confirmed by the isolation of 5 new feline cases from Central Italy, using Knott’s modified method, serology for Dirofilaria immitis antigen and PCR, by Traversa and colleagues from the University of Teramo (Veterinary Parasitology, 169 [2010] 128-132).

33 - Adult nematodes, 1 male and 1 female, have been recovered only in one cat from Kiev, Ukraina. Microfilaraemia is common in cats from Malaysia and South-East Asia.
34 - Dog constitute the main reservoir and main definitive host for *Dirofilaria repens*, with the highest prevalences being found in dogs from Sri Lanka (60%), Iran (61%) and Italy (30%, Po River Valley).

35 - A national survey carried out in France (1986) revealed that 1.3% of 5,502 dogs were parasitized by *Dirofilaria repens*.

36 - French Army dogs living in endemic areas in Southern France had 22% prevalence rate and 50% of these animals had mixed infection with *immitis*.

37 – Presence of *repens* microfilariae is common in dogs from Greece (22%) and Spain (9%).

38 - Microfilaraemia has been observed in dogs from all regions of Italy, mostly in Piedmont, Tuscany and Sicily.

   It is interesting to note that during the last 25 years in Italy the endemic area of *Dirofilaria repens* has considerably expanded.

   Mixed infection with *Dirofilaria immitis* has been seen in 12% of dogs affected by *Dirofilaria repens* in endemic areas of Italy where both parasites are present.

39 - Strict quarantine regulations seldom are an obstacle to the parasite’s life cycle, because the infection becomes evident (microfilaraemia) within 8-10 months or longer, after the mosquito bite, and the adult parasites can live 2 to 4 years.

40 - Suitable climates and presence of vectors can therefore facilitate the diffusion of this filarial worm.

41 – An increased number of autochthonous canine cases have been reported in recent years in new areas of Europe, including Germany, Slovakia, Czech Republic, Hungary, Ukraine, Russia, Austria, Switzerland, northern France and the Netherlands, as a consequence of climate changes together with increased pet travel.

42- Today, the highest prevalence in Europe is reported in Serbia, with 49.2% of dogs found affected by *D. repens* in a recent survey (2008), confirming 28 human cases recorded in the last 40 years.

**IMPORTANCE OF THE CASE HISTORY**

43 - Cats and dogs travel frequently from endemic to non endemic areas of Europe and viceversa. To effectively prevent mosquito-borne diseases, owners and veterinarians should be aware of the risks associated with the geographic movements of pets. Questioning the owner regarding history of travel and living areas of pets has become essential in order to obtain a correct diagnosis and effective therapy.
44 - To stress the importance of collecting all anamnestic data to build up a good ‘case history’, I often remind that my first encounter with *Dirofilaria repens* happened in a non endemic area, Aosta Valley (North-Western Italy), near the border with France and Switzerland.

45 - It was the case of a cat with a 3-year history of itching dermatitis previously residing for 2 years in Camargue (southern France).

The location – Camargue – and the presence of a dermatological syndrome unresponsive to previous therapies, led to a search that culminated in my first diagnosis of *Dirofilaria repens*. Knowing the former living area of the cat was determinant and helped to find an appropriate diagnosis and therapy!

**HISTORIC OVERVIEW**

46 - It is probably not a coincidence that the earliest documented report of subcutaneous dirofilariasis comes from southern France, and dates back more than 400 years.

47 - In 1566, Amatus Lusitanus (1511-1568), a Portuguese physician, reported the first clinic case of ocular filariasis in a 3-year old child in southern France that most probably can be attributed to *Dirofilaria repens*. His report suggests that similar cases were not uncommon in southern France at that time.

48 - Three centuries later, Italian ophthalmologist Addario (1885) removed a worm from the eyelid of a woman in Milan. The worm was named *Filaria conjunctivae* because of its location in the eye. Later on, when worms where submitted to identification, this name was dropped in favour of the current denomination, *Dirofilaria repens*, which is now recognized as cause of subcutaneous, subconjunctival and pulmonary nodules.

49 - Itching, swelling and tenderness of the affected site (arm, eyelid, chin, temporal area or testicle) are common in human subcutaneous dirofilariasis. Italy is the country most affected, recording more than 200 cases, followed by Sri Lanka, France, Ukraine, Greece and the Balkans.

**VETERINARY DISCOVERY**

50 - In veterinary medicine, *D. repens* was first described by Bonvicini in a dog from Bologna, Italy in 1910. The parasite was then speciated in France by Railliet and Henry (1911).
51- It was not until 1953 that the nematode was isolated again in nine adult specimens by two clinicians, Guilhon and Graber, in the subcutaneous tissues of dogs living in the Paris area of France.

52- Next year, in 1954, Giulio Ajmerito, Professor at Turin Veterinary School – who was by the way my teacher of Pharmacology - first recognized *D. repens* as a cause of pruritic dermatitis in dogs.

53 – In his Italian paper, a dog showing a chronic itching dermatitis was carrying *D. repens* microfilariae in the blood and was successfully treated with an arsenical medicament.

54 - Few years later, in 1957, subcutaneous dirofilariasis characterized by skin lesions, conjunctivitis and gastro-intestinal ailments was reported in dogs imported from Europe to Argentina.

55 - During the sixties the parasite was isolated again by Restani and colleagues in six dogs from central Italy affected by pruritic dermatitis relapsed after medication with corticosteroids and antibiotics.

56 - Dogs were successfully treated with an arsenic-based drug named Caparsolate, confirming that they were effectively infected by a filarial worm (Restani and colleagues, 1966).

57 – In 1987, Beaufils and Martin-Granel found a dog coinfected with *Hepatozoon canis, Leishmania* and *Dirofilaria repens* in southern France.

58 - Two other French authors, Cazelles and Montagner, observed in 1996 two dogs co-infected with *Leishmania donovani* and *Dirofilaria repens*.

59 - These findings might be discharged as anedotical, however they are important in the light of recently cumulated evidence that *Dirofilaria repens* is an opportunistic parasite often manifesting clinical signs in association with concurrent immune-surppressive conditions such as babesiosis, erlichiosis and leishmaniosis.

**CONTROVERSIAL PATHOGENICITY**

60 – Actually, *Dirofilaria repens* is not widely known to cause pruritic dermatitis, apparently persisting as a well kept veterinary dermatological secret for at least one century.

61 - However, there is scientifically recognized and widely published evidence that common signs of the infection in pets are itching (pruritus), papulae, erythema, alopecia, crusting, hyperkeratosis, lichenification and acantosis.
62 - Occasionally, subcutaneous nodules can be seen, made by a kyst enclosing an adult nematode.

63 - In most cases, however, no pathogenic signs are observed in animals carrying repens microfilariae.

64 - As a consequence, detection of D. repens microfilariae in dogs is still regarded by many (vets) as irrelevant and not requiring treatment, although medical therapy would greatly decrease the risk of infection to humans, and would help to eliminate cutaneous ailments in affected animals or to prevent their appearance or flaring.

65 - The pathogenicity of the nematode, in fact, is still poorly understood, mainly because: a) skin lesions appear only in a subset of infected dogs and are not predictable; b) the gastrointestinal signs and poor performance in symptomatic dogs are not strictly indicative of a filarial disease; c) classic adulticide and microfilaricide treatments seldom produce complete clinical recovery and parasitological eradication.

**CLINICAL SIGNS IN DOGS**

66 - Dogs living in rural areas or with access to outdoor environments are usually more affected since the risk of mosquitoes bite is higher.

67 - During summer and autumn, the larger number of circulating microfilariae microscopically observed in the blood increases the chance of cutaneous manifestations.

68 - Skin symptoms tend to recur seasonally in spring to autumn during the second-third year and to become persistent after the fourth year of infection.

69 - Pathogenic effects – either seasonal or permanent - are due to the cumulative action of increased number of microfilariae, increased number of adults, their auto-immune and toxic effects and re-infection.

70 - Affected dogs show first pruritus, manifested by localised scratching, licking and biting. The itch initially mild will become progressively severe, causing self-traumatic lesions.

71 - Dermatological signs in 100 consecutive canine cases of subcutaneous dirofilariasis were as follow: pruritus (100%), erythema (79%), papulae (62%), focal or multifocal alopecia (55%), hyper-
cheratosis (18%), crusting (14%), nodules (12%), acantosis (5%), eczema (3%), pyoderma (3%) and oedema (1%).

72 - Generally, 85% of dogs had at least one lesion on the posterior part of the body (lumbo-sacral region, hind limbs and perianal area).

73 - In the same 100 dogs group, symptoms and signs other than dermatological were as follow: conjunctivitis (46%), anorexia (35%), vomiting (26%), fever (25%), lethargy (20%) and lymphadenomegaly (10%).

74 - A similar pattern of collateral general signs has been noticed in dogs from Ukraine.

75 - Such general signs are not caused by *D. repens*. In fact, a recent report from Greece shows that there is no significant difference in sport performances between hunting dogs without skin lesions but carrying *repens* microfilariae and healthy non microfilaraemic dogs.

76 – So what causes the general signs? These are caused by concurrent factors/agents that help the manifestation, persistence and severity of clinical signs associated with subcutaneous dirofilariasis. On the other hand *Wolbachia* bacteria help *Dirofilaria immitis* manifestation, persistence and severity.

77- Eradication of underlying conditions followed by therapy with adulticide (melarsomine, Merial) and microfilaricide (ivermectin, Merial) drugs is essential to a complete cure and disappearance of microfilaraemia. Healing is confirmatory of the diagnosis!

78- Obviously, the recovery speed depends upon the duration of the disease, the age of the animal and the severity of lesions.

79 - Subcutaneous dirofilariasis should be included in the differential diagnosis of pruritic dermatitis and the exclusionary diagnosis of atopic dermatitis in pets living in endemic areas.

80- Monthly medication with spot-on solutions of imidacloprid/moxidectin (i.e. Advocate, Bayer) has preventive effect for heartworm disease and it also provide effective protection against *D. repens* microfilariae. The product may be administered throughout the year as prevention but it has not therapeutic effects against the adult worms.
81 - It is recommended that all dogs aged 6 months or more living in endemic areas, should be tested by Knott’s test, and medically treated if positive for repens microfilariae before being treated with moxidectin/imidacloprid.

**CONCURRENT INFECTIONS IN DOGS**

82 - In a group of 100 dogs diagnosed with Dirofilaria repens, babesiosis was the most common concurrent infection (95%) detected.

83 - Followed by canine granulocytic ehrlichiosis (40%), Leishmania (4%), Hepatozoon canis (2%), Ehrlichia canis (1%) and Ehrlichia platys (1%).

84 - It is acknowledged that Babesia and Ehrlichia species induce immune suppression favoring secondary opportunistic infections.

85 - Babesia and Ehrlichia infections show common signs of illness such as fever, lethargy, anorexia and vomiting. Interestingly, these are also the most prevalent collateral signs observed in dogs diagnosed with subcutaneous dirofilariasis: anorexia (35%), vomiting (26%), fever (25%) and lethargy (20%), thus confirming the claim of coinfection.

86 - A recent study from Germany seems to confirm these findings. In fact, Pingen and colleagues (2009) observed that 12% of dogs imported from Hungary carried repens microfilariae, and 19% were infected with Babesia canis, 11,6% with Anaplasma phagocytophilum, the agent of canine granulocytic ehrlichiosis and 1,6% with Ehrlichia canis. This study was presented at the International Conference of the World Association for the Advancement of Veterinary Parasitology (WAAP) in Calgary, Canada, on the 8th of August 2009.

**CLINICAL SIGNS IN CATS**

87 - Among 31 cats with dirofilariasis symptoms observed more often were: pruritus (100%), alopecia (77.4%), erythema (74.2%), papulae (51.6%) and crusting (29%).

88 - Symptoms and signs other than dermatological were as follow: anorexia (35.5%), lymphadenomegaly (32.3%), pale mucous membranes (29%), lethargy (16%), conjunctivitis (16%), pain (16%) and fever (10%).

89 - Concurrent infection with haemobartonellosis (Mycoplasma haemofelis infection) or Feline Infectious Anemia, which is transmitted by fleas or ticks, was recorded in 25 (80%) out of 31 cats examined
and its therapy with doxycycline (10mg/kg, for 20 days) greatly contributed to the clinical resolution.

90 - Doxycycline is important in the therapy of dirofilariasis because also eradicate the Wolbachia spp. bacteria symbiotic of adult worms, causing their sterilization and death.

**FACTORS INFLUENCING CLINICAL SIGNS**

91 - In epidemiologic surveys, subcutaneous dirofilariasis appears non symptomatic in a large number of animals, defined as healthy carriers.

92 - However, when the parasitosis is not eradicated, cutaneous manifestations may appear in a subset of patients, in a frame time ranging from few months to several years.

93 - For instance, in a personal follow-up case study (Alessandria, Italy) on a group of 9 untreated microfilaraemic and asymptomatic dogs, 4 (44%) out of 9 patients developed pruritic skin lesions within 5 months.

94 - This means that with time increased chances are to observe dermatological manifestations.

95 - Cutaneous signs are caused by (1) capillary embolization of microfilariae, (2) movement of adults in the subcutaneous tissues, (3) immunological-allergic reactions to parasitic stages L3-L5 and microfilariae and (4) toxins released by the parasites.

96 - Development of allergic and auto-immune reactions affecting the skin is common in parasitic diseases, including heartworm, depending on the number of parasites, the duration of the infection and the age and nutritional status of the animal.

97 - Experimentally infected dogs show microfilaraemia 6-8 months after inoculation even in the presence of only 1 male.

98 - Production of microfilariae continues for several months and last up to 3 years. Females can produce up to 5,000 microfilariae per day. The intensity of ‘parturition’ increases during spring and summer, with peaks in August and September, associated with cyclic manifestation of pruritus, erythema and alopecia.

99 - That’s why, may be also due to concurrent re-infection, subcutaneous dirofilariasis shows seasonal periodicity in the first 2-3 years.
100 - Nocturnal periodicity is not marked for *Dirofilaria repens* since at noon there is only 20-40% reduction in circulating microfilariae. As a consequence of this, blood for the search of microfilariae can be drawn from dogs under examination at any time during the day without risking false negative results.

101 - The adult worms reside in the subcutaneous tissues, where they live for as long as 4 years, and release microfilariae that circulate in the blood.

102- The combined action of adults and microfilariae prolonged over months and years, in association with triggering agents/factors causing transient or permanent immune-suppression, contribute to the manifestation of itching and dermatological signs.

103 - The opportunistic role of *Dirofilaria repens* might well explain the presence of asymptomatic carriers, the concurrent observation of non-dermatological signs and the development of dermatitis only in a subset of parasitized dogs.

104 - Comparatively, development and sexual differentiation of adult nematodes is facilitated in human patients affected by primary or secondary immunodeficiencies.

**IMPLICATIONS AND CONCLUSION**

105 – Frequently asked question n. 1: should dogs and cats with non symptomatic microfilaraemia be treated?

106 – Yes, if we are working in areas where suitable vectors exist and human cases have been reported.

107 - We should treat the infection in all affected animals, independently from the presence of clinical signs by 1) eliminating all concurrent predisposing/trIGGERING factors/agents detected, 2) and administering Melarsomine (Immiticide, Merial) to eliminate adults, 3) and Ivermectin (Ivomec, Merial) to eradicate microfilariae.

108 – Results of therapy are evident within 1 day (diminution of pruritus) and 2 months (disappearance of erythema and alopecia).

109 – The combined use of Knott’s test and antigen heartworm test produces 98% diagnostic accuracy.
It has been observed in human medicine that ‘the first clinical diagnosis of dirofilariasis is almost always wrong’ and that the condition is correctly diagnosed only in a second time.

A similar conclusion is also true in veterinary medicine, since 37% (in Italy) to 77% (in the Middle East) of dogs diagnosed with SD had previously received a different diagnosis and had been treated with other drugs (with no benefit or transient relief). Next time, please, don’t say “Not another itchy dog!” but (excited?!) “May be *Dirofilaria repens*?”

REFERENCES


