Babesiosis as an underlying factor influencing the severity and duration of perianal fistulas in three dogs

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SUMMARY

Perianal fistulas is a serious problem mostly affecting German shepherd dogs, which are predisposed to this condition as a result of breed and anatomical factors. A decreased cell-mediated immune response and similarities with the fistulous form of Crohn’s disease in humans have been recently noted. Consequently, a thorough search for the underlying factors seems advisable as part of the diagnostic work, with a view to the possibility of treatment by chemotherapy. The two 3-year old German shepherds and one 14-year old Pomeranian dog with perianal fistulas, described in the present report, were found to be carriers of Babesia spp., without specific clinical symptoms and signs of babesiosis, and consequently treated with imidocarb dipropionate once a week for 4 weeks. This therapy led to a complete recovery from the perianal fistulas, without subsequent relapses; no surgery was needed.

KEY-WORDS: Babesia canis - Babesia gibsoni - babesiosis - dog - perianal fistulas - imidocarb dipropionate.

RéSUMé

Les babésioses : un facteur sous-jacent influençant la sévérité et la durée des fistules périanales chez le chien. Par W. TARELLO.

Les fistules périanales chez le chien, le Berger allemand en particulier, représentent un très grave problème, qui est le résultat d’au moins trois facteurs : race, anomalies anatomiques et immunotaires. Récents études semblent confirmer que cette pathologie est caractérisée par une réduite réponse des lymphocytes et par des réactions inflammatoires chroniques semblables à la forme fistuleuse de la maladie de Crohn chez l’homme. Par conséquence on souligne la nécessité de préférer les traitements médicaux à la chirurgie.

Dans cette étude, deux Bergers allemands et un Loulou avec fistules périanales ont été trouvés porteurs de Babesia spp., sans signes particuliers de babésiose, et traités uniquement avec imidocarb dipropionate pendant 4 semaines, une fois par semaine au dosage conseillé (1 ml/25 kg). Le résultat fut la progressive et complète guérison des fistules, sans successives rechutes et sans recourir à la chirurgie.


Perianal fistulas (a.k.a. anal furunculosis) are considered a serious and frustrating problem primarily affecting German shepherd dogs [8, 14, 16]. The clinical signs include fever, depression, tenesmus, bleeding from the affected area, constant licking or biting at the site and diarrhoea [11, 16]. The breed predisposition is a result of anatomical factors, including the low tail carriage, the humidity of the perianal area and the high number of apocrine glands around the anus [7]. Nonetheless, these features alone cannot completely explain all the damages observed and the etiopathology of the condition remain uncertain [15, 16]. Treatment is difficult and frustrating, because relapses are frequent. Prednisone, dietary therapy, protracted courses of antibiotics and cyclosporine have been suggested, together with surgical methods involving sharp excision, cryosurgery and tail amputation to prevent recurrences [8, 10, 11, 17, 18]. A primary genetic defect has been suspected, but extensive analyses of pedigrees have not produced any data indicating a simple hereditary transmission [15]. Immune dysfunctions involving lymphocytic activity have recently been pointed out by some authors [10, 14]. In fact, the cell-mediated immune response, evaluated in vitro utilizing a lymphocyte blastogenesis test, was significantly decreased in 9 out of 33 dogs with perianal fistulas, when compared with healthy controls [14]. Links between thyroid status and the condition have been ruled out [14]. Several bacteria have been isolated from the affected tissues: Escherichia coli, Staphylococcus aureus and β-haemolytic Streptococcus strains [15].

However, long-lasting therapies with specific antibiotics, even if based on bacterial culture and sensitivity tests, are rarely efficacious in resolving the pathology and/or preventing relapses. A recent randomized controlled trial of cyclosporine for treatment of perianal fistulas [18], has produced promising results, but this drug is unfortunately very expensive and does not exclude recurrences.
Although the etiology of anal furunculosis remain obscure, it is now commonly accepted that breed predisposition and anatomical anomalies produce a combination of factors influencing the progression of the syndrome from cutaneous erosion to formation of invasive perianal fistulas [7, 10, 14, 16].

The three cases here described appear to confirm such observations and to provide further informations on the role of certain infectious agents in the condition.

**Clinical cases**

**DOG N. 1**

A 40-Kg, 3-year old pedigreed German shepherd male, certified dysplasia-free, was seen by referral in Ascoli Piceno (Central Italy) in April 1996, presenting symptoms consisting of mild weakness of the hind limbs, fresh blood in the stools and frequent licking of the perianal area. Three perianal fistulas each approximately 0.5-0.7 cm in diameter, were found on physical examination (Fig. 1). A mild serous ocular discharge was also observed.

A brief remission had been obtained following a 3-week long therapy with lyncomicin until 1 month before the visit. Then, episodes of weakness of the hind legs had recurred with increased frequency during the last month, even though appetite and posture at rest were normal. The owners reported that the dog had suffered from cyclic episodes of malaise since at a very early age. The test for Leishmaniosis (Leishcan 16) proved negative; the only biochemical abnormality of the serum was a slightly increased value of total proteins (TP = 7.81 g/dl) with particular reference to the globulin fraction (4.85 g/dl).

Fresh blood smears coloured with May-Grunwald-Giemsma and Wright stains revealed the presence of a low number of Babesia spp. organisms (Fig. 3).

On the basis of this microbiological finding it was decided to start treatment with a specific antibabesial agent (imidocarb dipropionate, Carbesia, Mallinckrodt Veterinary, 1 ml/25 Kg, sc.) while considering surgery as a future possibility. No other medical or dietary treatment was given. In a few days and after the first subcutaneous injection, the weakness of the hind legs and the ocular discharge disappeared. At the same time, the dog’s habit of licking the perianal area had significantly decreased and a direct inspection revealed an evident reduction of inflammation accompanied by mild signs of local healing and a white-yellowish exudative serous discharge. In consideration of this significant improvement, it was deemed necessary. Relapse did not occur during the following 7 days, repeated four times.

The progressive improvement of the general condition was associated with further cicatrization of the two residual fistulas. A control made 2 weeks later on fresh blood smears was negative for Babesia spp. and surgery was no longer deemed necessary. Relapse did not occur during the follow-wing four years the dog was kept under the author’s personal observation. Two very thin sinuses did remain but never progressed and no other treatment was necessary during this period.

**DOG N. 2**

A 45-Kg, 3 years old mixed German shepherd male living in the same geographical area as the previous case, was brought in for a routine vaccination in April 1999.

It was immediately apparent, on physical examination, that the dog was unwell: there were fever (39.7°C) and follicular conjunctivitis with mild mucouserous discharge. Multiple large ulcerative erosions, affecting a wide perianal area (Fig. 4) were noted, and diagnosed as the initial stage of perianal fistulas.

According to the precedent experience, an accurate search for Babesia spp. was carried out on fresh blood smears coloured with Wright and May-Grunwald-Giemsma stains and proved positive. The number of protozoa detected was low and consistent with the category of chronic subclinical infections. Again, imidocarb dipropionate (1 ml/25 Kg., sc.) was administered once a week for 4 weeks, and no other medical or dietary treatment was associated. Seven days after the first injection the erosions were markedly reduced (Fig. 5). Fourteen days later, at the time of the third injection, only one small lesion of around 0.5 cm. diameter could be detected (Fig. 6). On the day of the fourth injection (21th) the problem could be considered as resolved (Fig. 7). It is notable that the erosions healed without any topical aid. As in case n. 1, collateral signs, (such as conjunctivitis and fever), disappeared at the same time. The haematological control made 2 weeks later resulted Babesia-negative and during the following 15 months the dog did not suffer from relapses nor did it receive any other medical or surgical treatment.

**DOG N. 3**

An 8-Kg, 14-year old female Pomeranian dog was brought in by its owner, in July 1999, because its tail had spontaneously fallen off. During the preceding week, the owner had noticed several “holes” oozing yellowish-pink exudate, located between the insertion of the tail and the upper part of the anal region. On further questioning, the owner reported that in the previous two weeks the dog had been observed biting and licking the region, straining ineffectually and painfully at defecation, with stools showing bright red blood. For the past year, the animal had been suffering from a persistent dry cough and thick discharge from the eyes.

On examination, the entire perianal area was presenting a large (about 15 cm diameter) fungiform excrescence with a cribrous surface perforated by many crypts and fistulas (Fig. 8). Body temperature was 40°C, with enlargement of the submandibular and popliteal lymph nodes, bilateral follicular conjunctivitis and frequent coughing. The dog was walking with a wide, stiff and clumpsy gait.

A fresh blood smear was positive for Babesia spp. Treatment with imidocarb dipropionate (1 ml/25 Kg, s.c.) was immediately started at the rate of one injection every 7 days, repeated four times.
BABESIOSIS AS AN UNDERLYING FACTOR INFLUENCING THE SEVERITY AND DURATION OF PERIANAL FISTULAS IN THREE DOGS

FIGURE 1. — Dog n. 1. Perianal fistulas at the first visit.

FIGURE 2. — Dog n. 1. At halfway the course of the antibabesial treatment, signs of cicatrization and healing.

FIGURE 3. — Wright-stained blood smear showing different intra- and extracellular structures morphologically resembling *Babesia gibsoni*. 1: one ring and three comma-like forms in a single erythrocyte. 2: two merozoite-like forms. 3: one small piriform body (x 100).

FIGURE 4. — Dog n. 2. Initial observation of the affected site with ulcerative erosions recognizable as the first stage of perianal fistulas.

FIGURE 5. — Dog n. 2. Seven days after the first treatment: marked reduction of the lesions.

FIGURE 6. — Dog n. 2. Fourteen days later, (at the time of the third antibabesial injection) : only a small lesion (0,5 cm. in diameter) can still be observed.
FIGURE 7. — Dog n. 2. On the 21th day of treatment (fourth injection) the condition could be considered as resolved.

FIGURE 8. — Dog n. 3 (Pomeranian), at its first visit. The tail is missing. Ulcers and crypts burrowing into the depth of the connective and muscular structures above the anus, showing as a fungiform excrescence.

FIGURE 9. — Dog n. 3, 7 days after the first injection of imidocarb dipropionate: the cicatrization is under way.

FIGURE 10. — Dog n. 3, 21th day: Reduction in size of the area of the lesions; beginning of re-epithelization (arrow).

FIGURE 11 — Dog n. 3. 12-month follow-up: advanced healing; the hair has grown back to a good extent.
An improvement could already be observed when the dog was brought in for the second injection (day 7). Temperature was down at 39°0C, the coughing had ceased and the conjunctivitis had greatly improved. The lesions in the perianal area were granulating well without any topical therapy (Fig. 9). On the day (14) of the third injection, it was found that the diseased area was well circumscribed by the surrounding skin and connectival tissues, with no super-imposed exogenous infection. The animal was much livelier and could walk with an almost normal gait. On the day (21) of last treatment, the temperature was 38°5°C, with further healing of the lesions (Fig. 10). The gait was almost normal. A control fresh blood smear was negative for *Babesia spp.*

The last direct control of the dog was made 12 months later (August 2000) : the perianal lesions had healed completely, there were no recurrences and the hair had grown back (Fig. 11). The animal was presenting no relapses and, despite of the advanced age, was lively and in good health. The owner reported that no further treatment had been given.

**Discussion**

Three canine cases of anal furunculosis/fistulas, all associated with *Babesia spp.*, have been described. The first two dogs were German sheperds, where the disease is common — as already noted — for breed and predisposing anatomical factor of the low tail carriage. The third dog, in which the condition had produced a gross mutilation (fall of the tail), was a Pomeranian. All three animals benefited from therapy with imidocarb dipropionate, with no associated treatment (systemic, topical or dietary).

The recognized similarities between the clinical features of canine anal furunculosis and those of the fistulous form of Crohn’s disease in human [6] imply that perianal fistulas in dogs are today considered as an immune-mediated disease, requiring a complete individual anamnestic and clinical evaluation before taking a decision for surgery [11, 14]. The defect being immunological rather than anatomical, surgical excision and tail amputation can likely be unsuccessful [16], as proven by the prevalent insuccess and recurrencies after surgical treatment [8], with ensuing poor prognosis of the condition. A thorough search for underlying diseases (with consequential chemotherapy) is suggested today as the proper answer to the problem.

In the progress of time, trauma due to foreign bodies, abscess formation in the anal sacs and fecaliths in the anal crypts have been considered, but eventually ruled out [14], as possible causes of anal furunculosis.

Recent studies [6, 14] strongly indicate an auto-immune etiopathology : the clinical features of chronic inflammation, ulceration and sinus formation of the perianal tissues in the affected dogs are tantamount with the fistulous form of Crohn’s disease in humans [6], an auto-immune condition where the immune system is continously activated and stimulated in maintaining a chronic non-specific inflammation [19, 22].

Cyclosporin treatment of perianal fistulas in dogs and fistulous Crohn’s disease in human has been shown to have a beneficial effect in both species [10, 17, 18, 19] by inhibition of the proliferation of activated T-helper lymphocytes, thus reducing the production of interleukin-2.

As for other auto-immune diseases, (e.g. systemic lupus erythematosus [SLE] and rheumatoid arthritis [RA]), corticosteroids have also been found beneficial for symptom relief during long-term courses. Unfortunately, recurrence of lesions following cyclosporin or corticosteroids treatment are common. Relapses after cyclosporin treatment for Crohn’s disease are well documented [21]. Furthermore, repeated treatments with these medicaments involve a heavy financial burden, affordable only by wealthy owners; whereas chemotherapeutic preparations (such as imidocarb dipropionate, diminazene aceturate, phenamidine isethionate) are, costwise, much more accessible. A recent report [18] has also described cases of anal furunculosis with no response to cyclosporin, which finally required surgical intervention.

The three dogs reported in this study, suffering from perianal fistulas, were found to be carriers of *Babesia spp.*, without specifics signs of babesiosis, and consequently treated with imidocarb dipropionate once a week for 4 weeks. This therapy led to a complete recovery from the perianal fistulas without subsequent relapses. These results are notable since the therapy of this condition is considered difficult and the risk of recurrence is common. To this writer’s knowledge, a diagnosis of babesiosis in dogs with perianal fistulas has never been previously reported in literature. The evidence of a subclinical *Babesia spp.* infection in these dogs is not in contrast with recent observations of immune-mediated defects related with perianal fistulas, because babesiosis is considered as a disease that can cause secondary allergic responses and immune dysfunctions [2]. A recent study shows that there is a well-defined association between perianal fistulas and colitis in German shepherd dogs [11]. Gastrointestinal and circulatory disturbances are other features of chronic *Babesia* infections [4].

This report does not intend to establish a direct cause/effect liaison between babesiosis, as primary and/or unique cause, and perianal fistulas. However, babesiosis certainly was an existing co-factor for the severity and duration of the illness and following specific treatment with imidocarb dipropionate clinical improvement and recovery were rapid and satisfactory, even thought this could be considered as a merely *ex juvantibus* criterium. Furthermore, *Babesia spp.* protozoa could no longer be observed at blood controls carried out later : this apparently was the main difference observed between blood smear examination of the same dogs, while with anal furunculosis and when clinically cured. Signs of babesiosis, such as conjunctivitis, episodic diarrhoea and weakness, ceased at the same time as the remission of perianal fistulas and this was apparently due to the only treatment that had been given. Canine babesiosis, that has been reported in domestic dogs throughout the world, can be caused by two different species, *Babesia canis* and *Babesia gibsoni* [2, 3, 9, 23, 25] and a recently detected, small Babesia microti-like species [26].

This recent discovery demonstrates that the fauna of piroplasms occurring in dogs is more varied than assumed so far. Symptoms produced may thus be different from those caused
by *B. canis* and *B. gibsoni*. Babesial protozoa are substantially differentiated on the basis of the infected host species and of the morphology of the parasite, particularly as to its size [3, 5, 9, 20]. *Babesia canis* organisms are pleomorphic, with size about 4 µm and shape varying from ameboid to ring forms. *Babesia gibsoni* is also pleomorphic, and far smaller (1–2.5 µm) [4, 9]. Characteristically, trophozoites are comma-like, annular, spherical or oval (Fig. 3). At the invasive stage ("émerozoitèes"), they are extra-erythrocytic and can be seen on the external surface of the red blood cells, or floating free in the plasma [2]. Both species have been reported in Italy [5, 20, 24, 26]. Despite appropriate staining technique and thorough examination of blood smears, parasites cannot always be demonstrated and their detection is more difficult in chronically infected, asymptomatic carriers.

Diminazene aceturate, phenamidine isethionate and imidocarb dipropionate are effective therapeutic agents for canine babesiosis. A comparison of imidocarb dipropionate with other therapies for perianal fistulas would be premature here, on the basis of three cases only and without randomized studies on larger series as obtainable in institutions larger than an individual veterinary practice. It is of note, however, that this drug is unexpensive, safe, easy to inject subcutaneously and does not entail a prolonged duration of therapy. It can be even used for the prevention of babesiosis (and ehrlichiosis, too). Breed and anatomical peculiarities predispose German shepherd dogs to anal furunculosis; these factors cannot be modified to the extent of preventing the condition. On the contrary, immune-mediated abnormalities that involve infectious agents and can be treated, must be considered with attention in the clinical practice, with a view to non-invasive treatment with a better prognosis.

The data collected in three canine cases would seem to indicate that species of the *Babesia* genus are likely to be the infectious agents favouring the condition and that therapy with imidocarb dipropionate, a specific antibabesial medicament, can help towards remission of the disease and prevention of its recurrence.

Although human babesiosis has never been associated with Crohn’s disease, the therapeutic role of malaria chemoprophylaxis [1] against the latter condition is nowadays acknowledged, together with the observation of a high incidence of arthralgia and ocular inflammation among these patients [22]. The results of the present study do not contrast the current therapeutic approach to the problem, and seem to confirm the comparative relationship already made between perianal fistulas in dogs and Crohn’s disease in humans.

The main conclusion is that babesiosis should be added to the potential causes of anal furunculosis. Therefore, examinations of blood smears (before and after enrichment) should be recommended as a laboratory routine in the differential diagnosis of perianal fistulas.

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**References**


