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Diseases that affect the anal area in dogs were first described\textsuperscript{1} en 1945. However in 1961 the relationship the anal fistula tract and the male, middle age German shepherd and Irish Setter were observed\textsuperscript{1}.

Canine perianal fistulas also known as anal forunculosis, anusitis, anorectal abscesses, perianal fissures\textsuperscript{1}, is a chronic debilitating condition characterised by progressive ulceration, fistulas tract and concomitant tissue inflammation of the anal, perianal, peri rectal and base of tail region down to the hind limb. Occasionally the rectal lumen may also be affected\textsuperscript{18}.

The aetiology of the disease has not yet fully elucidated although the primary caused is now recognised to be immune mediated linked to granulomatous inflammatory bowel disease (IBD) in human and in dogs\textsuperscript{18}.

It mainly affects middle age males of the breeds German Shepherd and Irish Setter\textsuperscript{1}, but it is seen in many other breeds\textsuperscript{2} such as Labrador, old English sheep dog, Bull dog and Collie\textsuperscript{18}.

Inflammation and ulceration of the area is reflected by the following symptoms:

- Pain
- Tenesmus
- Dy szchezia
- Anorectal mucopurulent discharge
- Pyotraumatic dermatitis of the region
- Constipation
- Hematochezia
- Incontinence
- Licking
- Coprophagia
- Vocalisation at defecation\textsuperscript{19}
- Anal Fibrosis
- Lordosis
- Changes in character
- Systemic signs of illness and weight loss\textsuperscript{18}

Fistulas can extend several centimetres to reach the rectal lumen, anal glands to the base of the tail.

The severity of symptoms can be defined by the extent of the affected area in 360\textdegree around the anus\textsuperscript{18}.
For many years the disease was associated with different theories:

1) Infection in the anal glands, as origin for formation of fistulas.

2) Defects of conformation, anatomical hypothesis: in the German shepherd, the angle relative to the position of the tail is particularly low compared to other breeds, this means low aeration and high humidity of the perianal region and stagnation of faecal material in the form of small fecalithes which accumulated in the crypts of the anal mucosa, this predisposes to the development of fistulas in the skin.

3) Histological hypothesis: The distribution of apocrine glands in the perianal region. Determines that the German Shepherd has a high density of apocrine sweat glands and hair follicles in the region.

In the late 90’s a link to the disease was made with certain types of immune disorders of the type of chronic colitis, food intolerances and, recently, Crohn disease in humans. Therefore one could say that although two new theories emerged they were related:

4) Hypothesis of association with chronic colitis

Colitis-proctitis could favour certain conditions for the formation of fistulas:

- Existence of chronic mucosal injury secondary to diarrhoea.
- Activity of antigenic components of the enteric lumen.
- Inflammatory perpetuation common to every colonic disease.

5) Immunomediated hypothesis

It has been demonstrated in an immune disorder associated with a German shepherd IBD and a bacterial overgrowth by an increase in the expression of interleukins2, 5, 12p40, TNFα and TGFβ in intestinal tissue. Other studies that underlying diseases such as babesiosis could affect the immune system and promote perianal fistula formation.

**Diagnosis:**

Clinical history, physical exam and overall clinical picture makes the diagnosis of perianal fistulas relatively simple.

The differential diagnosis could include:

- Fistulas secondary to anal gland abscessation
- Mucocutaneous acantholysis bullosa
- Deep pyoderma
- Neoplasia (Adenomas / adenocarcinomas)
- Candidiasis

Initially this appears as pinkish spots which then ulcerated and fistulate. Channelling fistulas are usually...
deep\textsuperscript{10} and travel towards the rectum, anal glands and the perirectal tissue.

Cytology:
Cytology of the fistula contents (abundant neutrophiles, macrophages and intra and extra cellular bacteria) is usually compatible with a pyogranulomatotic process. In all cases the results of culture and sensitivity often reveal numerous enteric bacterial species such as Escherichia coli and Proteus mirabilis as well as staphylococci and streptococci\textsuperscript{19}.

Histopathology:
The lesions are characterised by the infiltration of lymphoid cells, plasma cells and eosinophiles indicating immune activation. The histopathology is similar to that of the lesions in human patients with Crohn’s disease\textsuperscript{18}.

**Therapeutical management:**

Historically medical management was directed at correcting the local environment of the perineum with an attempt to increase ventilation and reduce moisture. This meant shaving the area, amputating the tail, regular washing and the use of antiseptics or antibiotics topically or systemically. The outcome of these therapies was considered palliative. The surgical options for treatment included surgical excision or cauterization of the fistula either chemically (Lugol solution, Silver nitrate) as well as by high or low temperatures, these were considered radical and relapses were common and there were numerous complications. Some of this was also true for Crohn’s disease in human.

Among the most common complications for the use of the radical methods were:

- Anal estenosis
- Loss of sphincter tone
- Faecal incontinence
- Dyschezia

According to a systematic review of studies reporting success of various surgical treatments and their complications the following was found\textsuperscript{18}:

<table>
<thead>
<tr>
<th>Method</th>
<th>Success</th>
<th>Complications (incontinence/relapse)</th>
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</thead>
<tbody>
<tr>
<td>Chemical cauterisation</td>
<td>87%</td>
<td>20% incontinence y 17% recurrence</td>
</tr>
<tr>
<td>Fulguration up to 180°</td>
<td>high</td>
<td>average</td>
</tr>
<tr>
<td></td>
<td>270°-360°</td>
<td>low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>48-97%</td>
<td>45% of relapses</td>
</tr>
<tr>
<td>Saculectomy and excision</td>
<td>variable</td>
<td>71% incontinence y 50% relapse</td>
</tr>
<tr>
<td>Amputation of the tail</td>
<td>up to 80%</td>
<td>40% of relapses</td>
</tr>
</tbody>
</table>

It is considered essential the saculectomy together with the surgical act to decrease the prevalence of complications and recurrences\textsuperscript{1,18}. Evidently, according to this review, surgical procedures are accompanied by a high rate of complications and relapses. The establishment of dietary and medical therapy may substantially increase the rate of surgical success and decrease the frequency of relapses in the medium and long term. Post-surgical medication must included stool softeners such as the plantago ovata.

The emergence of new theories on the pathogenesis of the disease was accompanied by therapeutic alternatives.

Recently in veterinary medicine due to the possible immune mediated involvement, alternatives such azathioprine, cyclosporine, tacrolimus or combination of the above\textsuperscript{10}.

Immunosuppressive treatment may also be combined with surgical treatment when the lesions are very large or with antibiotics if the discharge is significant.

The most successful therapeutic drugs incur, in general, a greater cost disadvantage.
Since 1997 in a study by Matews and Sukhiani, looked at the efficacy of cyclosporine (calcineurin inhibitor) in the resolution of the problem. Its immunosuppressor effect is achieved by inhibiting the activation of T-lymphocytes confirming the immunological basis of perianal fistulas. The concomitant administration of cyclosporine with ketoconazole allows reduction of the dose of cyclosporine, while minimising their side effects and reducing costs.

Azathioprine has the advantage of being cheaper than cyclosporine but it is more effective and has fewer side effects than prednisone. Azathioprine acts by removing the T-cell mediated response, thanks to their purine analogue metabolites that disrupt the synthesis of DNA and RNA. The addition of metronidazole to azathioprine has sped up the resolution process but has not improved the percentage of remissions.

Summary of some of the therapeutic options:

- **Cyclosporine**
- **Topical Tacrolimus**
- Azathioprine + metronidazole + surgery
- Prednisone + hypo-allergenic diet
- Cephalosporine + Sulphasalazine + Metronidazole + diet rich in AGE.
- Diet rich in ω3 and ω6
- Laser Application
- Cryosurgery (liquid nitrogen)
- Diverse surgical options (fulguration, scissions, chemical cauterization)

The use of tacrolimus topical can be justified to reduce costs compared to cyclosporine and to supplement or continue the treatments with this. Tacrolimus acts blocking the lymphocyte T activity (blocking the production or suppressing the expression of some interleukins) in a similar way to the cyclosporine, despite it is 10 to a 100 times more powerful than this and with less undesirable effects. These characteristics make the tacrolimus to be a good option in certain cases as has the advantage over the cyclosporine not to produce systematic immunosuppression, to be cheaper and easier to administer and to have a more direct action, only in the affected area.

Another study on the combination of medical and surgical treatment, Lombardi et al have achieved one year after surgery, 87% of complete or near complete resolution with perioperative feeding with a diet of fish and potatoes (high % of omega 3 and 6) combined with antibiotic cephalexin as the basis pre-post surgical and antibiotic metronidazole against Giardia, anaerobes and sulphasalazine as an immunomodulator and anti-inflammatory, inhibiting the production of leukotrienes. The surgery performed was a saculectomy and bloc removal of the injured area. Antibiotics were administered before (from 1 to 180 days) and after surgery (from 30 to 60 days). Only 20,7% of the dogs kept some mild clinical signs and intermittent. The authors attribute this success to the anti-inflammatory treatment, combined with a diet high in fatty acids and radical surgery. The variation in the duration of this treatment before and after surgery depended on the severity of symptoms and compliance by the owners.

**Recommended doses of different treatments:**

- **Cyclosporine**, at a dose of 2,5-3,5 mgs./kg. every 12 hours, 2 hours before of after meals. Cyclosporine with ketoconazole at 1,5 mgs./kg every 12 hs + 10 mgs./kg/day orally respectively. Ketoconazole interferes with the enzyme cytochrome P450 reducing the degradation of cyclosporine and decreasing the dose to be administered.

  The dose of cyclosporine may vary according to the hepatic metabolism of the individual. The ideal is to maintain therapeutic blood levels between 400 and 600 ng/ml. The daily treatment typically extend about 3 months and then move to an alternate day pattern of gradually lower dose.

- **Azathioprine**, 2 mgs./kg/24 hs./orally, to obvious improvement. Then switch to alternate days for 12 weeks and then 1 mg/kg every 48 hours during 12 months. This dose will be reduced before if myelosuppression signs appear.
Prednisone, 2 mgs./kg./day, the first two weeks, then another two weeks at half dose and discontinue according to evolution.

Tacrolimus, starting with the 0,1% ointment, once a day and pass to the 0,03% concentration according to evolution or irritation.

Metronidazole, 15 mgs./kg./ twice daily orally.

Sulphasalazine, 15 mgs/kg./three times daily orally.

Bibliography