ABSTRACT

A 6-year-old, male, neutered, English Mastiff dog was presented for a second opinion due to chronic pruritus. The patient had been on methylprednisolone and chlorphenamine for four years. The diagnostic investigations included: swabs for bacterial and mycology culture, hair plugs for dermatophyte culture, acetate tape strips and deep skin scrapes, skin biopsies for dermatohistopathology, biochemistry, haematology, endocrinology, serology for canine scabies using enzyme-linked immunosorbennt assay (ELISA) testing and serology for allergen specific IgE antibodies. The history and the diagnostics confirmed the diagnosis of canine atopic dermatitis. This case report details the treatment with lokivetmab, which is a caninised monoclonal antibody drug. At periods of flare ups, additional treatments were prescribed, such as systemic glucocorticoids and oclacitinib in order to manage the clinical signs. The treatment showed good response to the overall treatment management during the three year period of this atopic patient.

Key words: canine atopic dermatitis; CAD; caninised monoclonal antibody; lokivetmab; mAb

INTRODUCTION

Canine atopic dermatitis (CAD) is a common skin disorder defined as a hereditary predisposition to develop pruritic inflammatory skin disease associated with type I hypersensitivity [21]. Whilst the disease can be present in dogs from as early as 4 months old to as late as 7 years old [21], it mainly affects those between 6 months old and 3 years old, with 75% of the cases within this age range [2].

CAD is characterised by pruritus and secondary skin lesions. Common skin lesions involve localised pruritus of the ears, lips, peri-palpebral region, digits, axillae, inguinal and perineal regions. The primary lesions include erythema and papules and salivary staining of hairs caused by licking. Many secondary changes lead to chronic lesions which mainly appear due to chronic self-trauma. Such lesions include excoriation, alopecia, lichenification and hyperpigmentation [9].
IL-31 is a known cytokine for its pruritogenic effects in dogs [7] monkeys [17] and mice [1]. There are many treatment options to manage CAD, however there is no cure. Topical treatments include: glucocorticoid (triamcinolone) sprays [4] and ointments, tacrolimus [3], shampoos, emollient emulsifiers, moisturisers, occlusive dressings, cleaners and diets (either home prepared or commercially prepared). Systemic treatments include: glucocorticoids, specific immunotherapy, cyclosporin A (CsA), antihistamines, nutraceuticals such as essential fatty acids [9] oclacitinib [16] and lokivetmab [22]. Lokivetmab is a caninised monoclonal antibody (mAb) that binds and neutralizes canine Interleukin (IL)-31. Recent studies have shown good efficacy of lokivetmab for the management of CAD [2, 18, 22, 25].

CASE PRESENTATION

Signalment, history and presenting complaint

A 6-year-old, male, neutered, English Mastiff dog, with body weight of 45 kg and a body condition score 6/9 was presented for a second opinion due to chronic pruritus. The onset of pruritus started at the age of 2 years old by licking the paws, scratching and shaking of the ears. The owner estimated the pruritus score to be 6/10 and was described as: moderate pruritus that itches/scratches often [14]. The patient had been on methylprednisolone (Meditro; Zoetis) 0.09 mg.kg$^{-1}$ po once daily and chlorphenamine (Piriton; GlaxoSmithKline) 4 mg per dog po twice daily for four years. There were periods of good pruritus control and periods of flare ups. The patient was not up to date with a preventive parasitic treatment. An acute diarrhoea was only present at the age of 1 and was fully resolved with symptomatic treatment.

Physical examination

The physical examination was performed while the patient was muzzled, therefore the mouth was not assessed.

General physical examination

The patient appeared nervous but alert and responsive. The heart rate was found to be normocardic 80 bpm, the respiratory rate was normopnoeic 20 bpm and the rectal temperature was normothermic 38.5 °C. The rest of the general examination was unremarkable.

Dermatological examination

During the consultation the patient occasionally scratched his ears and tried to reach the paws and the medial aspect of the thighs bilaterally through the muzzle. On otoscopic examination, both auricles had moderate diffuse erythema on the convex and concave aspects. The external auditory canals appeared moderately erythematous and the lateral aspect of the tympanic membranes were normal and intact. There were no signs of stenosis, cerumen accumulation nor signs of purulent otitis. The clinical examination of the thoracic and pelvic ventral carpal, interdigital spaces and ventral pedal and the medial aspect of the thighs revealed spotty hyperpigmentation, lichenification, partial alopecia and diffuse scarlatiniform erythema of the skin. No ectoparasites were seen and there were no signs of pyoderma. There were no other primary or secondary dermal lesions on the rest of the body.

ETHICAL CONSIDERATIONS

Written consent for permission to publish this case report was obtained from the owner of the patient. The author declares no known conflicts of interest.

CASE MANAGEMENT

Problem list and differential diagnoses

The main problem was the pruritus with the accompanied skin lesions. The initial differential diagnoses included with descending order of importance with CAD to be top on the list due to its chronicity and clinical presentation followed by: food hypersensitivity, contact dermatitis, folliculitis, infectious or parasitic otitis, fungal and yeast infections such as dermatophytosis, malassezetic dermatitis and candidiasis. Apart from CAD, another hereditary disease was considered, i.e., the familial canine dermatomyositis. Lastly, parasitic infestations such as mites (Sarcoptes scabiei var. Canis and Demodex), fleas (Ctenocephalides felis), and lice (Cheyletiella and Heterodoxus spiniger) were also considered.

Initial treatment plan

Given the long history of the patient, it was advised to proceed with diagnostics in order to get a diagnosis, thus
enabling it to be managed appropriately. Initially it was advised to taper the methylprednisolone to 0.045 mg.kg\(^{-1}\) po for a week and then to cease, whilst continuing with the chlorphenamine treatment at a higher dosage, at 8 mg per dog po three times daily, and perform diagnostics a month later in order to do a washout period before the diagnostics. Additionally, it was advised to bathe the patient with a soothing hypoallergenic shampoo (Ermidra; Vetruus) twice per week. Lastly, an endo-parasitic preventive treatment was prescribed with milbemycin oxime 0.5 mg.kg\(^{-1}\) po and praziquantel 5 mg.kg\(^{-1}\) po (Milbemax; Elanco) and an ecto-parasitic preventive treatment was prescribed, i.e., Fluralaner (Bravecto; MSD) 31.1 mg.kg\(^{-1}\) po every three months.

Diagnostic investigations and results

Due to the temperament of the dog all the procedures were done under a general anaesthetic.

Pre- and intra-operative details

The patient was premedicated with medetomidine (Sedastart; Animalcare) at 5 μg.kg\(^{-1}\) intramuscularly (im) and methadone (Synthadon; Animalcare) 0.25 mg.kg\(^{-1}\) im. After ten minutes, sedation was judged to be good and propofol (PropoFlo Plus; Zoetis) at 4 mg.kg\(^{-1}\) was used by slow intravenous injection. The trachea was intubated with a size 12.0 mm cuffed endotracheal tube. The anaesthesia was maintained with sevoflurane (SevoFlo; Zoetis) vaporised in 100% oxygen delivered via a non-rebreathing breathing circuit.

### Table 1. Results of haematological and biochemical examination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>62 × 10(^{9}).l(^{-1}) ↓</td>
<td>160—500 × 10(^{9}).l(^{-1})</td>
</tr>
<tr>
<td>WBC</td>
<td>5.3 × 10(^{9}).l(^{-1}) ↓</td>
<td>6.0—15.0 × 10(^{9}).l(^{-1})</td>
</tr>
</tbody>
</table>

**HAEMATOLOGIST’S COMMENTS**

- WBC: Morphology unremarkable
- RBC: Normocytic normochromic
- Platelets: Moderate clumping, count would be higher
- Sample quality: Good

### Table 2. The IgE and IgG positivity for food allergens

<table>
<thead>
<tr>
<th>FOOD ALLERGENS</th>
<th>IgE</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Lamb</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Chicken</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Turkey</td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>Egg</td>
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<td>Negative</td>
</tr>
<tr>
<td>Soya been</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Corn</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Wheat</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Rice</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Carrot</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

WBC—white blood cells; RBC—red blood cells

DGGR—1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester
Blood work was advised for haematology, biochemistry and endocrinology in order to rule out systemic dermatoses, but also to look for possible hepatopathy due to the long term use of glucocorticoids. A mild increase of the creatinine, creatine kinase and pancreatic lipase were not significantly important (Table 1). The platelets count was low, however there were clumps on the microscopic examination which ruled out a possible thrombocytopenia and the mild leukopenia was not significant (Table 1). The remaining haematology, biochemistry, total thyroxine (T4) and canine thyroid stimulating hormone (TSH) were within the normal range. A serum sample was obtained for canine scabies using enzyme-linked immunosorbent assay (ELISA) testing and it was ruled out.

Serum samples were obtained for the initial allergy screen for allergen specific IgE- antibodies which included testing for allergy to fleas, food, Malassezia IgE, perennial (indoor) and pollen (outdoor) allergens. On the basis of positivity in the initial screen, the serum samples were tested for pollen allergens and food allergens (Table 2). The serology allergy testing for the pollen showed positives for privet and borderline positivity for oak. For food allergens, the IgE positives were egg and rice and the IgG positives included beef, lamb, chicken, turkey, soya bean, corn, wheat, rice and carrot (Table 2).

Skin sampling

Swabs were taken for bacterial and mycology cultures, and hair plugs for dermatophyte cultures. Acetate tape strips (scotch test) and deep skin scrapes for cytology were taken from the interdigital spaces, from the external auditory canals and from the medial aspect of the thighs.

The aerobic, anaerobic, mycotic and dermatophyte cultures did not grow any pathological microorganisms apart from normal cutaneous microbiota. In cytological microscopy examination, no ectoparasites, arthrospores, bacteria, yeasts, nor nucleated material were seen.

Full thickness skin samples were taken by 6 mm punch biopsy technique from each medial thigh for dermatohistopathology. The skin was closed with a single cruciate pattern using nylon (Ethilon; Ethicon) size 3.0 metric sutures which were removed 10 days postoperatively without complications. The histological diagnosis for both samples was perivascular dermatitis, lymphoplasmacytic, multifocal, mild with epidermal hyperplasia, orthokeratotic hyperkeratosis and mild dermal oedema which was consistent with secondary chronic degenerative changes of the skin due to poor control of the disease.

Upon completion of the surgery, the sevoflurane was discontinued and the patient was moved to recovery. The patient was injected with atipamezole (Sedastart; Animalcare) 25 μg.kg\(^{-1}\) im in order to reverse the sedative effects of medetomidine. Once the swallowing reflex had returned the trachea was extubated. Following the general anaesthetic, meloxicam (Metacam; Boehringer Ingelheim) 0.2 mg.kg\(^{-1}\) subcutaneously (sc) was administered for analgesia.

The patient was discharged from the hospital on the same day with an Elizabethan collar to protect the wounds. Oral formulation of meloxicam 0.1 mg.kg\(^{-1}\) po was prescribed for three days starting the first dose 24 hours after the initial injectable dose.

**DIAGNOSIS**

Taking into consideration the patient’s long history of pruritus, the positive response to glucocorticoids, the histological report and the positive results on serological ELISA testing, the author reached the diagnosis of CAD.

**TREATMENT AND OUTCOME**

For the management of environmental allergens, the patient was prescribed lokivetmab (Cytopoint; Zoetis) 1.11 mg.kg\(^{-1}\) sc, every four weeks. Additionally, a highly hydrolysed hypoallergenic diet (Hill’s prescription z/d Dog Food) was advised by gradual introduction in order to manage the food allergens. Lastly, the owner was advised to keep up to date with preventive parasitic treatment and hypoallergenic shampoo twice a week. The patient was reviewed four weeks later, where the clinical signs were fully resolved and the same lokivetmab dose was repeated. It was proposed to repeat the next lokivetmab dose five weeks later, however the pruritus and subsequently the dermal signs returned soon after the fourth week. Therefore, it was agreed with the owner to administer the lokivetmab every four weeks in order to manage the clinical signs sufficiently. It was advised to stop the chloramphenicine treatment at that point.
Later on, in springtime, there was a flare up of CAD due to the increased pollen levels, despite having the lokivetmab every four weeks. The clinical signs were resolved with a short acting glucocorticoid, dexamethasone (Dexadreson; MSD) 0.08 mg.kg⁻¹ im.

For three years and up until the time of writing this case report, the patient has been on the same dose of lokivetmab injections every four weeks, hydrolysed diet, preventive parasitic treatment and regular hypoallergenic shampoo baths. In periods of flare ups and in particular during the springtime, the clinical signs are managed with short acting systemic glucocorticoid injections such as dexamethasone at a dose of 0.16 mg.kg⁻¹ im and in some cases with oclacitinib (Apoquel; Zoetis) 18 mg.kg⁻¹ po once daily for two weeks.

**DISCUSSION**

The methylprednisolone was replaced with lokivetmab due to the side effects that glucocorticoids can cause in long term use, but also due to the inadequate response to the former treatment. Lokivetmab has high efficacy with 87.8% reduction of pruritus associated with CAD and can be administered every 4—8 weeks depending on the patient’s needs, with rare side effects [25]. A study by Moyaert et al. demonstrated that lokivetmab at a minimum dose of 1 mg.kg⁻¹ sc, repeated at monthly intervals, provided onset of effect in reducing pruritus within one day and continued efficacy for one month [22]. In the Marsella et al. [18] study, prednisolone, CsA, oclacitinib and lokivetmab were compared for the clinical efficacy on severity of dermatitis and pruritus, and also the effects on trans epidermal water loss and hydration. Lokivetmab showed that it can prevent flare ups when given prior to challenge and also that it has some positive effects on skin barrier parameters. A more recent study by Flick et al. showed that a single subcutaneous injection of 2 mg.kg⁻¹ lokivetmab produces a significant suppression of pruritus starting 3 hour post-treatment and be sustained for 42 days [5].

Another treatment option for management of CAD is CsA. This treatment was not considered by the author due to the high cost, the need for daily medicating, the immunosuppressive component and that CsA should be reserved for severe CAD cases where pruritus is inadequately controlled by standard antipruritic treatments [9]. Furthermore, lokivetmab’s antipruritic efficacy is more pronounced than CsA, with fewer adverse effects [22].

Flare ups were managed by the author with dexamethasone injections and oral oclacitinib. Takahashi et al. demonstrated topical glucocorticoid treatment and systemic oclacitinib (inhibitor of proinflammatory cytokines) combination therapy for CAD patients is more effective than oclacitinib monotherapy [27]. A human comparative study showed that topical glucocorticoids achieved effective skin concentrations greater than the effective concentration achieved by oral corticosteroid treatment [20]. Based on these two studies, the author will consider the use of topical glucocorticoids instead of systemic ones in order to increase the skin concentrations by using fewer glucocorticoids in shorter periods of time.

Allergen-specific IgE serological (ASIS) testing was used by the author to aid the diagnosis due to the lack of in-house intradermal testing (IDT). Both techniques have identical interpretation of the results, however in a serological approach it is better to use techniques employing standardised procedures and high thresholds to ensure good specificity [9]. Both ASIS and IDT are designed to aid in the diagnosis of CAD and also to aid in the formulation of allergen specific immunotherapy (ASIT). It is also very important to remember that ASIS should not be used for screening, as false positive results are found in non-atopic patients [10]. Furthermore, there is poor correlation between ASIS and IDT testing [6] and the success rate of ASIT based on both methods is not significantly different [24].

ASIT, also known as anti-allergen vaccination or desensitisation, is a treatment option for managing the aeroallergens but not the food allergens [9]. This treatment approach was not considered due to the seasonal positive pollen allergens. It would not be beneficial for the patient to receive this treatment all year round when the pollen aeroallergens are only present during the spring and summer. Moreover, immunotherapy takes considerably longer to be effective. After 9—18 months, only 10—20% of the patients showed a complete cure and 50—80% of the animals showed significant improvement [8].

CAD shows identical clinical signs whether caused by food or environmental allergens [11], therefore the feeding diet that the patient receives plays an important role in the management of this disease. Cutaneous adverse food reactions and in this case the immune IgE and IgG mediated
hypersensitivity revealed positive results in serological allergy testing. Although many laboratories offer serological testing for IgE and IgG antibodies for food allergens, it is good to bear in mind that many studies have shown that this method is not a reliable way of diagnosing adverse food reactions [23]. Currently allergen specific IgE serology and intradermal allergy testing do not confirm canine adverse food reactions [12, 13]. The gold standard for diagnosis and management of food allergy is an elimination home cooked diet trial. However, this method can be very time consuming and extremely difficult to meet the nutritional requirements [26] of a dog and therefore the author did not consider this approach. The author, instead, recommended a commercial highly hydrolysed diet where the allergenicity is decreased [23]. J oh a n s e n et al. study showed some promising results for patch testing on the diagnosis of food allergy, however this is still in the experimental stage [15].

This case was managed with a good outcome. Lokivetmab was the main drug that kept the CAD under control, along with the diet and the baths. Flare ups are expected with CAD and it is a matter of managing them in the best possible way. There are many available treatment options, however each treatment must be tailored to the patient’s need and to the owner’s compliance.

ACKNOWLEDGEMENTS

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