Pemphigus foliaceus

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Aetiopathogenesis

Desmosomes are complex structures involved in intercellular adhesion and signalling in epithelia. In canine pemphigus foliaceus (cPF) IgG auto-antibodies target desmosomal proteins inducing acantholysis and blister formation in the subcorneal and/or intragranular layers of the epidermis. Vesiculation is accompanied by neutrophilic infiltration that results in clinically visible pustules. Desmocollin 1 is a desmosomal transmembrane glycoprotein involved in intercellular adhesion and is a major autoantigen in cPF. (Bizikova 2012). That some canine breeds are predisposed to develop disease suggests genetics may underlie pathogenesis, whereas environmental factors may trigger development of clinical signs in predisposed individuals (Olivry 2009). Diet is implicated in people. Compounds in food may be similar to drugs (thiols, isothiocyanates, phenols, tannins). Drug triggered PF occurs in patients predisposed to PF. Human drug induced PF is usually associated with exposure to medications with chemical structures that can contribute to the activation of proteolytic enzymes in skin. In dogs and cats PF is suspected to be associated with a variety of medications eg cimetidine, cephalexin, amoxicillin-clavulanic acid, ampicillin and trimethoprim sulfa. Cutaneous drug reactions usually develop around seven days after the first administration of a drug. If a patient has been previously exposed to the drugs, reqctions are quick and usually occur within 24 hours of drug re-exposure (Tater 2010). UV exposure from the sun is a potential trigger for PF (Tater 2010). Most cases are idiopathic.

Diagnosis

Clinical appearance

In all species, clinical signs consist of pustules that evolve rapidly into erosions covered with crusts.
Skin lesions are usually bilaterally symmetrical, especially on the face (dorsal planum of nose, periorbital region and pinnae). Involvement of non-haired skin (nasal planum and footpads) rules out many diseases eg staph pyoderma, demodicosis and most dermatophytes. Lesions may be pruritic (25–50% of dogs). Footpad involvement is seen in one third of dogs with PF and rare canine patients exhibit lesions restricted solely to footpads. The pustules in PF are usually large and confluent. Many hair shafts can protrude from these pustules, in contrast to pustules in bacterial folliculitis where only a single hair comes from each pustule. Alopecia and generalised exfoliative erythroderma is seen occasionally (Olivry 2006).

Cytology

Diagnosis of PF in animals begins with demonstration of acantholytic keratinocytes in impression smears of intact pustules (Olivry 2006). In PF a mean of 226 acantholytic cells per mm2 of biopsy, vs 12/mm2 in biopsies from superficial bacterial folliculitis. Acantholytic cells were 183x more likely to be present in PF. The presence of rafts of acantholytic cells occurred in PF (23/50) more than in superficial folliculitis (1/47) (Kuhl 1994).

Histopathology

Superficial epidermal or follicular pustules rich in neutrophils and acantholytic keratinocytes.
I will leave the details of this to Dr Geoff Orbell.

Treatment and outcome

General approach

The treatment of PF involves the use of many immunomodulating drugs which can have significant side effects. It may be worth balancing the desire for perfect control of disease with a recognition of the effect of these

medications on quality of life for the patient and caregiver burden for the client. Most patients do not die of the disease itself, their owners make the call for them based on cost, the need for frequent treatments and vet visits and quality of life of their pets. I generally start by trying to obtain complete remission with quite aggressive treatment, then slowly tapering medication, but I do commonly vary this approach based on the client and the patient response. A 2004 retrospective study from the Uni of Pennsylvania showed a case fatality rate of approx. 60%. Of the 43 dogs included in the study, 17 were alive at the end of the study period and 26 had died (Gomez 2004). Duration of treatment and the number of complications were found to be significant factors associated with survival of dogs. Of the dogs that diet, 18/26 (69%) were euthanased because of complications directly related to the skin disease, including inability of treatment to induce remission, poor quality of life as perceived by the owner, or factors directly attributable to the adverse effects of treatment.

Oral medication

Prednisolone/dexamethasone

Petra Bizikova's 2015 paper in the Veterinary Dermatology Journal described the use of high dose oral glucocorticoids (prednisone or prednisolone) at 10mg/kg once daily for 3 consecutive days, followed by a reduced dose of glucocorticoid (2mg/kg/day). The proportion of dogs achieving complete remission in the first 12 weeks of treatment was significantly higher for the pulse group of 18 dogs (61%) vs the traditional group of 20 dogs (15%) and that a lower average maximal oral glucocorticoid dosage was given to the pulse group vs the traditional group, resulting in lower adverse drug events. At the ESVD conference in 2021 Petra Bizikova gave a presentation in which she clarified that this pulsing should be repeated no more than once weekly and no more than three times. She also clarified that the between pulse dose she is now using is 0.5–1mg/kg of prednisolone daily.

Prior to this, more traditional dosing was much lower, e.g. in the 2004 Gomez paper described below. Mean dosage of prednisone monotherapy was 2.2mg/kg PO sid. Only 25% of dogs receiving prednisone received concurrent sucralfate or an H2 blocking agent at the initiation of treatment. There was no significant difference in the survival rates between dogs that received and those that did not receive treatment with gastric protectants. Adverse effects observed in dogs included PU/PD, seizures, pancreatitis and death. The most frequent complications associated with initial treatment included severe PU/PD (40%), weight gain of >10% (33%), muscle wasting and lethargy (28%) and increased ALT (9%). Less frequent adverse effects included liver failure, diabetes mellitus, pancreatitis, calcinosis cutis, blood dyscrasias, weight loss, behaviour changes, diarrhoea, demodicosis, seizures and DIC (Gomez 2004).

Apoquel (oclacitinib)

Oclacitinib is a selective JAK1 inhibitor targeting the signalling of cytokines involved in pruritus and inflammation. It preferentially targets the activation and function of Th2 cells. Its immune modulatory effects on numerous cytokines have prompted investigation of its use in non-allergic, cytokine mediated inflammatory and auto immune or immune mediated diseases in dogs either as monotherapy or an adjunctive treatment (Marsella 2023). Oclacitinib was used as monotherapy for control of a presumed auto-immune subepidermal blistering dermatosis and complete resolution was obtained at 0.5mg/kg twice daily after two weeks. Relapse was observed when the regimen was reduced to once daily (Aymeric 2017). Oclacitinib was also useful in a case of drug induced pemphigus vulgaris at 0.5mg/kg twice daily (Martinez 2022).

Ciclosporin

Oral modified ciclosporin combined with glucocorticoids achieved CR in 9/11 PF dogs during the induction phase in this study (Chong 2022).

Nicotinamide

Nicotinamide exhibits cholinomimetic effects due to both stimulation of acetylcholine release and inhibition of acetylcholinesterase (Grando 2004).

Tetracycline

Tetracyclines have an inhibitor effect on chemotaxis of neutrophilic and eosinophilic granulocytes, besides which tetracyclines possibly improve the strength of the dermo-epidermal layer (Toth 2001).

Chlorambucil

Commonly used as a steroid sparing drug at an induction dosage of 0.1mg/kg sid (Rosser 1995).

Azathioprine

Purine antagonist. Six mercaptopurine is methylated by thiopurine methyltransferase (TPMT). Side effects myelosuppression (toxic effect on haematopoeitic cells), cutaneous neosporosis, liver toxicity (Toth 2001). Mean dosage of azathioprine was 1.3mg/kg sid (Gomez 2004).

Topical medication

Glucocorticoids

Localised skin lesions may be managed with topical glucocorticoids (Tater 2010).

Tacrolimus

Tacrolimus is an immunomodulator which inhibits calcineurin, an important factor in the intracellular signal transduction pathway. Inhibition of calcineurin results in suppression of antigen presenting T cells, inhibition of the production and release of inflammatory cytokines including many interleukins, GM-CSF, TNF-alpha and INF-gamma. In this study two dogs with PE both had excellent responses (Griffies 2004).

Feline pemphigus

Aetiopathogenesis

The exact target in feline pemphigus has not yet been elucidated, unlike canine PF. It may be Dsg-1.

Clinical appearance

The main difference in appearance between canine and feline PF is the involvement of the nailfolds in cats.

Treatment

The high dose pulse therapy of glucocorticoids described for dogs is not effective in cats (pers comm P Bizikova). In cats, the use of oclacitinib is off label. Effective control of non-allergic cutaneous inflammatory conditions with oclacitinib is limited to a publication of a 13-year-old cat with PF (1mg/kg PO bid). (Carrasco 2021). A 50% clinical improvement was observed after seven days and was maintained at a dose of 0.5mg/kg PO every 12 hours (Marsella 2023).

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