



Mark Craig BVSc CertSAD MRCVS

Mark Craig qualified from Liverpool University in 1985. After 5 years in general veterinary practice, Mark spent three and a quarter years as resident in dermatology at the Royal Veterinary College, where he gained his certificate in small animal dermatology. Since leaving the college in 1993, he has built up **Re-Fur-All Referrals**, a veterinary dermatology referral service in the South of England and the West Midlands.

Mark has written and lectured extensively on animal skin diseases, translated dermatology articles and text books from French to English, and presented papers at national and international dermatology congresses.

Re-Fur-All Referrals, 31 Porchester Road, Newbury, Berkshire, RG14 7QH

Tel: 01635 35600

E-mail: mark@markcraig.co.uk



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Diagnosis and management of pemphigus foliaceus in dogs

Pemphigus foliaceus (PF) is one of a group of uncommon auto-immune diseases known as the pemphigus complex. Many studies have been conducted to determine the major antigen(s) for PF in the dog but so far without success. Drugs, allergic skin disease, and environmental factors are believed to be triggers. Canine PF is a pustular, crusting dermatosis, principal differentials for which include superficial bacterial folliculitis, demodicosis, dermatophytosis and other pemphigus conditions. Diagnosis is based on clinical history and signs, cytology and skin biopsies. The treatment of choice is immune suppression and the prognosis is variable.

Key words: Pemphigus, crusting, canine, auto-immune, dog

Introduction

Pemphigus foliaceus (PF) is one of a group of uncommon auto-immune diseases known as the pemphigus complex (Figures 1-4). The condition was first reported in the dog in 1977 (Halliwell and Goldschmidt 1977) and is now considered the most frequently occurring auto-immune dermatosis in dogs (Vaughan *et al.* 2010). The incidence of PF in the general canine population is unknown but was reported to be 2% of referred cases in one dermatology practice (Rosenkrantz 2004).

Pathogenesis

The pathogenesis of human PF involves the production of auto-antibodies against a target protein, desmoglein (dsg) 1, found in desmosomes, the adhesion molecules of keratinocytes (Miller *et al.* 2013¹). Many studies have been conducted to determine the major antigen(s) for PF in the dog but so far without success (Olivry 2006). Some studies (Suter 1993; Iwasaki *et al.* 1997) have suggested that, as in human PF, dsg1 is the target auto-antigen in canine PF, but it is currently thought that dsg1 is only a minor auto-antigen for canine PF (Olivry 2006). Canine PF appears to be clinically, histologically and immunologically heterogeneous (Olivry 2006).

Triggers

Drugs

In humans, drugs are a recognised trigger for pemphigus foliaceus (Wolf *et al.* 1991). Drug eruptions are notoriously hard to prove but there have also been a number of reports describing an association between drugs and PF-like signs in the dog. PF-like cutaneous adverse drug eruptions following application of metaflumizone and amitraz (Promeris Duo, Fort Dodge) (Oberkirchner *et al.* 2011); fipronil, amitraz and S-methoprene

(Certifect, Merial) (Bizikova *et al.* 2014); and dinotefuran, prapoxifen and permethrin (Vectra 3D, Ceva Animal Health) (Bizikova *et al.* 2015) have been reported. In other reports, reactions to trimethoprim-sulphonamides, cephalexin and oxacillin have been proposed (Medleau *et al.* 1990; White *et al.* 2002).

Allergic skin disease

An association with allergic skin disease has also been proposed. 11.6% of dogs diagnosed with PF had a diagnosis of concurrent atopic dermatitis (Gomez *et al.* 2004). In another study, 15 out of 40 dogs (37.5%) diagnosed with PF had a history consistent with allergic dermatitis, with flea allergy documented in 9 (60%) of these dogs (Vaughan *et al.* 2010). Definitive proof for such an association is hard to establish. A drug reaction, either induced or triggered, cannot be ruled out given that these dogs had all been treated many times with different drugs.

Environmental factors

The role of environmental factors in triggering flares of canine PF has been reviewed (Olivry 2006). Lesional scores of PF worsened in the summer in 10 out of 12 dogs, and improved in the winter (Iwasaki and Yamakita-Yoshida, 2003). Seasonal exacerbation was not, however, found in an epidemiological study involving 66 dogs with PF (Pascal *et al.* 1995). Experimentally, findings from experimental studies using ultraviolet (UV) light radiation suggested that further investigation of UV exacerbation of canine superficial pemphigus was warranted (Iwasaki and Maeda, 1997). Diet has been implicated in human forms of pemphigus (Ruocco *et al.* 1996; Tur and Brenner 1998) particularly in relation to thiols (e.g. in garlic, onion, leek and chive), isothiocyanates (e.g. in mustard, horseradish, turnip, radish,

cabbage, cauliflower and Brussel sprouts), phenols (e.g. in mango, cashews and many food additives), and tannins (e.g. in tea, coffee, and certain fruits including apples, pears and bananas). There have been anecdotal reports of food-induced PF in dogs.

Insect vectors (e.g. black flies), viruses, local heat, and humidity have also been suspected of being predisposing factors in human PF (Lombardi *et al.* 1992) – Table 1.

Table 1. Environmental factors suspected of being predisposing factors or triggers in human PF

- Ultraviolet light
- Insects
- Diet
- Viruses
- Heat and humidity

Signalment

Most cases occur in middle-aged or older dogs but any age can be affected (Vaughan *et al.* 2010). In one review of 37 dogs (Ihrke *et al.* 1985¹), signs presented initially at 5 years or less in 65% of cases. Any breed may be affected but some reports have shown the English Bulldog, Chow Chow, Akita, Dachshund, Cocker Spaniel and Labrador Retriever to be over-represented (Ihrke *et al.* 1985¹; Vaughan *et al.* 2010). No sex predilection has been confirmed but one report showed a significant male bias (Gomez *et al.* 2004).

Clinical signs

The head and face are predisposed, seen in over 80% of cases, and typically the first areas to be affected, especially the dorsal muzzle, planum nasale, peri-ocular skin and ears where lesions are typically bilaterally symmetrical (Figures 5, 6). In the largest case series, lesions were restricted to the face in 15 out of 91 dogs (16%) (Mueller *et al.* 2006). In the same study, footpads were involved in a third of cases, and lesions became generalised in 60 dogs (66%). Crusting was present on the trunk in 58% of dogs with generalised lesions (Figures 7, 8). Occasionally, lesions may be restricted to the footpads (Ihrke *et al.* 1985²)

Pruritus and pain are variable, and systemic signs may include anorexia, pyrexia, depression, weight loss and lymphadenopathy (Olivry 2006). Canine PF is a pustular, crusting dermatosis. The primary lesion may start as a papule, progressing quickly into a pustule. Large pustules are characteristic (Figure 9), and extensive areas of erosions, yellow crusts,



Figure 1: Pustules and crusts on the neck of a 2-year old entire male Staffordshire Bull Terrier with pemphigus foliaceus



Figure 5: Severe crusting and alopecia on the head of a 10-year old neutered male Jack Russell Terrier with pemphigus foliaceus



Figure 2: Papules, pustules and crusts on the ventral abdomen, legs, tail and perineal region of an 8-year old entire male Cavalier King Charles spaniel with pemphigus foliaceus



Figure 6: Severe focal crusting and alopecia on the ears and dorsal neck of a 10-year old neutered male Jack Russell terrier with pemphigus foliaceus



Figure 3: Papules, pustules and crusts on the ventrum of an 8-year old entire male Cavalier King Charles Spaniel with pemphigus foliaceus



Figure 7: Severe generalised focal crusting and alopecia in a 10-year old neutered male Jack Russell Terrier with pemphigus foliaceus



Figure 4: Severe generalised crusting and alopecia in a 10-year old neutered male Jack Russell Terrier with pemphigus foliaceus



Figure 8: Severe focal crusting and alopecia of the ventral abdomen of a 10-year old neutered male Jack Russell Terrier with pemphigus foliaceus

scaling, epidermal collarettes (Figure 10) and post-inflammatory alopecia may ensue (Figures 7-9).

Lesions do not assume a mucocutaneous distribution and the mouth is not usually involved. Nasal depigmentation may occur, but much later than in, for example discoid lupus erythematosus, leading to increased susceptibility to damage by ultraviolet light. Pedal lesions include fissures in the footpads and crusting, and may be so severe as to cause lameness.

The course of canine PF is unpredictable with some cases progressing rapidly and others waxing and waning. Secondary staphylococcal skin infection is often a feature (Figure 10).

Differential diagnosis

The principal differentials include superficial bacterial folliculitis (SBF), demodicosis, dermatophytosis and other pemphigus conditions. Cutaneous lupus, dermatomyositis, cutaneous adverse drug reaction, and leishmaniosis (in appropriate geographical regions) should also be considered. Pustules in canine PF are typically large with many protruding hair shafts (Gross *et al.* 2005). In SBF, pustules tend to be small with a single protruding hair shaft (Olivry 2006). In SBF, lesions typically do not start on the face or involve the ears. Nor do they cause crusting on the footpads (Miller *et al.* 2013²).

Diagnosis

This is based on clinical history and signs, cytology and skin biopsies. Differentials should be eliminated. A pustular disease that does not behave like staphylococcal pyoderma should raise suspicion for PF. Careful assessment of all drug therapy, systemic and topical, should be made.

Impression smears of intact pustules should be taken to look for acantholytic keratinocytes (separated, free-floating, rounded and deeply staining epidermal cells which may occur singly or in 'rafts'), well-preserved neutrophils, and an absence of bacteria (Figure 11). Neutrophils in pyoderma are more likely to be degenerate. Microbial culture should be performed to assess for pyoderma but it should be remembered that secondary bacterial infection can accompany PF, leading to the presence of intra-cellular and extra-cellular cocci.

Skin biopsies reveal classic, but not pathognomonic, histopathology of subcorneal pustules with acantholytic



Figure 9: Multiple large, coalescing pustules on the ventral neck of a 2-year old entire male Staffordshire Bull Terrier with pemphigus foliaceus.



Figure 10: Epidermal collarettes, papules, pustules, alopecia, crust and hyperpigmentation on the ventral abdomen, inguinal region and peri-vulval region of an 8-year old entire female cross-breed.

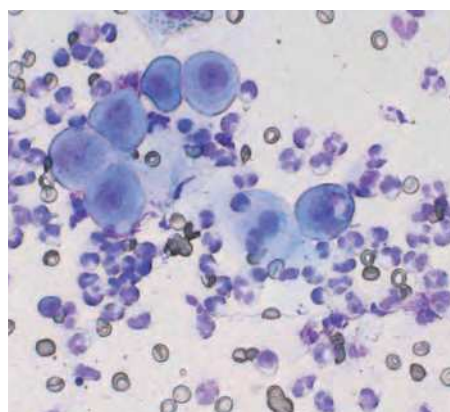


Figure 11: Acantholytic cells, neutrophils (degenerate and non-degenerate) and some cocci. (Photo courtesy of T. Whitbread, Abbey Veterinary Services)

cells and neutrophils. Eosinophils may also be present. In one study, dogs with concurrent disease, a history of allergy, or a history of adverse effects associated with immunosuppressive therapy were significantly more likely to have an eosinophilic infiltrate (Vaughan *et al.* 2010). Although acantholytic pustules can also be found in dermatophytosis, and acantholysis has been reported in dogs with bacterial skin infections, a high number of free-floating epidermal cells may be more suggestive of PF than other dermatoses (Kuhl 1994).

Skin biopsies can also be submitted for direct immunofluorescence or immunohistochemical staining. However, the classical immunological abnormalities are not always apparent, and evidence from such procedures can be supportive but not diagnostic of canine PF (Miller *et al.* 2013^{1,3}).

Treatment

Immune suppression is considered the treatment of choice for canine PF.

Glucocorticoids

The usual treatment for generalised canine PF involves systemic glucocorticoid steroids. Large doses of steroid are required initially. Oral (methyl)prednisolone, 2-6 mg/kg, every 24 hours, or in two divided doses, is effective in resolving lesions in most dogs. Once the condition has stabilised, the dose can be reduced gradually to the lowest possible alternate-day level that gives adequate control. In many cases, such high doses of steroid are poorly tolerated (Table 2) and other treatments should be considered. However, none of these treatments is licensed for use in the dog and severe adverse reactions may occur.

Oral steroid pulse therapy has recently been described in which dogs received at least one 'pulse' consisting of prednisone or prednisolone (10 mg/kg once daily) for 3 consecutive days followed by a lower dose (target < 2 mg/kg/day) of the steroid (Bizikova and Olivry 2015). More dogs in the 'pulse' group (61%) achieved complete remission in the first 3 months than dogs in the 'traditional' group (15%). The number of adverse drug events was identical in both groups.

Topical steroids may be effective in localised forms of canine PF (Rosenkrantz 2004). They may be used alone or in association with systemic therapy.

Nicotinamide and tetracycline

Nicotinamide (niacinamide in American texts)* and tetracycline combinations are sometimes helpful (Table 3). Mechanisms of action are unknown but both are believed to have anti-inflammatory and immunomodulatory properties (White *et al.* 1992; Edginton *et al.* 2011). This author has successfully used nicotinamide without tetracycline to reduce or eliminate the need for more potent immunosuppressive therapy. Response to therapy occurs within about eight weeks. Nicotinamide (not to be confused with other forms of vitamin B3, niacin and nicotinic acid) is available from specialist vitamin and mineral suppliers.

Azathioprine

Azathioprine* (Imuran, Aspen) is a cytotoxic drug used most commonly in cases of canine PF that are poorly controlled with glucocorticoids. A dose of 1.5–2.5 mg/kg can be given alongside (methyl)prednisolone until lesions resolve. The dose of both drugs is then reduced slowly with the aim of giving a maintenance dose of around 0.5 mg/kg of azathioprine one day and the lowest possible effective dose of prednisolone the next day. Precise dosing, of course, needs to be customised to each individual patient. Due to a lag phase, clinical improvement with azathioprine may occur only after 3–6 weeks of treatment (Miller *et al.* 2013⁴).

Azathioprine is well-tolerated by most dogs but in the largest case series reported to date, results of combination treatment with prednisolone and azathioprine were comparable to results with prednisolone therapy alone (Mueller *et al.* 2006). The major adverse effect is myelosuppression (anaemia, thrombocytopenia and leukopenia), and dogs should be monitored with blood and platelet counts, every few weeks initially and every 3–4 months once the condition is stable (Rosenkrantz 2004). Other reported adverse effects include hepatopathy, pancreatitis, diarrhoea, vomiting, skin rashes and alopecia. Long-term therapy may be associated with demodicosis, pyoderma and dermatophytosis due to immunosuppression.

Chlorambucil

Chlorambucil* (Leukeran, GlaxoSmith-Kline) is another cytotoxic drug. Oral dosage in dogs with PF is 0.1–0.2 mg/kg every 24–48 hours. Myelosuppression, anorexia, vomiting and diarrhoea have all been reported, although chlorambucil is considered less toxic than azathioprine. It is available only in a 2 mg tablet.

Secondary pyoderma, if present, should be treated with an appropriate dose of a suitable antibiotic.

In view of the association of diet with some cases of human pemphigus, a 6–8 week restricted 'hypoallergenic' diet is perhaps indicated in canine pemphigus.

* unlicensed for use in the dog.

Prognosis

Prognosis is very variable. Drug-induced forms may resolve once the drug has been withdrawn. Other varieties may require life-long therapy. For dogs unable to tolerate immunosuppressive therapy, the prognosis can be very poor. In one study, a

Table 2. Some of the side-effects associated with systemic glucocorticoid steroid use in the dog

Acute side-effects possible with high-doses of glucocorticoids

- Gastrointestinal ulceration and perforation
- Myopathy
- Pancreatitis

Other side-effects

- polyuria/polydipsia
- increased appetite and weight gain
- behavioural changes (lethargy, depression, increased aggression, hyperactivity)
- panting
- diarrhoea
- increased susceptibility to infection: urinary tract, respiratory tract, skin
- musculoskeletal abnormalities
- metabolic and endocrine disturbances
- alteration of haematological and biochemical parameters

Table 3: Suggested dosage of nicotinamide and tetracycline in canine pemphigus foliaceus

Criteria	< 10 kg	> 10 kg
Nicotinamide (vitamin B3)	250 mg every 8 hours	500 mg every 8 hours
Tetracycline	250 mg every 8 hours	500 mg every 8 hours

satisfactory response to treatment was seen in 93% of 31 cases treated (Rosenkrantz 2004). In another report, 52% of 88 dogs underwent complete remission (Mueller *et al.* 2006). In a third study, 18 out of 43 dogs were euthanased because of treatment failure, unacceptable treatment side-effects, or poor quality of life (Gomez *et al.* 2004).

Summary

Pemphigus foliaceus (PF), considered the most frequently occurring auto-immune disease in dogs, is a pustular disease which typically causes a severe crusting dermatosis. The differential diagnosis of PF includes superficial bacterial folliculitis, demodicosis and dermatophytosis. Definitive diagnosis is usually based on histopathology. Treatment typically involves immunosuppressive doses of systemic glucocorticoid steroids. When steroid therapy is poorly tolerated, alternative treatments such as azathioprine, and chlorambucil, and nicotinamide and tetracycline may be given. The prognosis is variable, often poor.

Other auto-immune diseases

Pemphigus disorders

Other, much less common disorders of the pemphigus complex include pemphigus vulgaris, paraneoplastic pemphigus, pemphigus vegetans and pemphigus erythematosus.

Pemphigus vulgaris (PV)

This is a more severe condition than PF, affecting classically the oral cavity and mucocutaneous junctions (Carlotti *et al.* 2000). Onset may be sudden or gradual, and lesions are vesiculobullous initially, progressing to erosions and ulcers. Systemic signs include pyrexia and anorexia. Lesions occur deeper in the epidermis than in PF, and acantholytic cells are rarely seen on cytology.

Paraneoplastic pemphigus (PNP)

Only two cases of confirmed canine PNP have been reported. The condition in man carries a very poor prognosis.

Pemphigus vegetans

Only three canine cases have been reported.

Pemphigus erythematosus (PE)

PE has features of both PF and discoid lupus erythematosus (DLE) and may, actually, be a variant of PF.

Histopathology and direct and indirect immunofluorescence are used in the diagnosis of these rare varieties of pemphigus. Treatment is similar to that recommended for PF. The prognosis for PV is poor. Tetracycline and nicotinamide (White *et al.* 1992) and topical tacrolimus (Griffies *et al.* 2004) have been reported to be helpful therapies for PE.

Lupus

Systemic lupus erythematosus (SLE)

This is a multi-system disorder involving dermatological signs in 40–50% of cases in the dog (Scott *et al.* 1983). Canine SLE is very rare.

Discoid lupus erythematosus (DLE)

DLE, also known as cutaneous lupus erythematosus (CLE), is characterised in the dog by nasal depigmentation, loss of normal cobblestone architecture, erythema and scaling, and, in chronic cases, erosions, ulcers and crusts (Griffin *et al.* 1979). Systemic signs are absent. Clinical signs are believed to be exacerbated, or possibly induced, by ultraviolet light. In one report, 0.3% of cases presented to a veterinary dermatology clinic were diagnosed with

canine DLE (Scott *et al.* 1983). Diagnosis is based on history, clinical signs and histopathology. The prognosis is good, and potent immunosuppressive treatment is often unnecessary. Treatment may involve sunlight avoidance, sunscreens, tetracycline-nicotinamide combinations (White *et al.* 1992), vitamin E (400 IU every 12–24 hours), essential fatty acids, topical and systemic glucocorticoid steroids, and topical tacrolimus (Miller *et al.* 2013 ⁵). Reports of therapeutic efficacy are largely anecdotal.

Vesicular cutaneous lupus erythematosus

This is an ulcerative condition affecting the ventrum of middle-aged to older Shetland Sheepdogs and Rough Collies (Jackson 2004). Onset is usually in the summer months. Response to immunosuppressive therapy is variable.

Exfoliative cutaneous lupus erythematosus

This has been described in the German Short-Haired Pointer (Bryden 2005). Onset is typically in young adults, initially affecting the muzzle, pinnae and dorsal trunk, and later, the limbs and ventral trunk. Lesions are characterised by scaling and alopecia, ulceration and crusting, sometimes with lymphadenopathy, stiffness, and pyrexia. SLE is an important differential but the condition does not fulfill the criteria for SLE. Response to immunomodulatory therapy is reported to be variable and the prognosis is guarded (Mauldin *et al.* 2010).

Alopecia areata

Alopecia areata is an uncommon disorder involving patches of non-scarring focal or multi-focal hair loss. Pathogenesis is complex and thought to be influenced by genetics, hormones, and environmental factors such as stress, vaccination and infection (Olivry *et al.* 1996; Alkhalifah *et al.* 2010). Definitive diagnosis is based on the presence of well-circumscribed areas of non-inflammatory alopecia and characteristic histopathology. Multiple skin biopsies from early lesions are recommended. 60% of canine cases are thought to resolve spontaneously with complete hair regrowth (Miller *et al.* 2013 ⁶).

Auto-immune sub-epidermal blistering diseases

These are a group of very rare disorders characterised by auto-antibodies to components of the basement membrane resulting in separation of adjoining

structures, accumulations of serum or clear transudates, and formation of vesicles and/or bullae (Miller *et al.* 2013 ⁷). Examples include acquired junctional epidermolysis bullosa, bullous pemphigoid, epidermolysis bullosa acquisita, linear IgA bullous disease, mucous membrane pemphigoid, and type 1 bullous systemic lupus erythematosus. Diagnosis is based on history, clinical signs, histopathology, and direct and indirect immunofluorescence. The prognosis is generally uncertain given the limited experience in recognising and treating these disorders in dogs.

Canine uveodermatological syndrome

This is a rare disorder of concurrent granulomatous uveitis and skin depigmentation typically involving the face and sometimes the footpads, scrotum, anus and hard palate. Histopathology reveals a lichenoid dermatosis. Failure to correct eye lesions may lead to blindness. Long-term immunosuppressive therapy is usually indicated, and dermatological response should not be used to assess response to therapy (Miller *et al.* 2013 ⁸).

References

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March 6-26, 2017

Canine atopic dermatitis: Have we even scratched the surface?



Mark Craig

BVSc CertSAD MRCVS

Canine atopic dermatitis (CAD) is one of the most common conditions encountered by vets. In this course, we will explore the pathogenesis of this complex, challenging phenomenon, along with clinical signs, diagnosis, and treatment. Reasons for the apparent increased incidence of CAD, and the likelihood of developing safe, effective, alternative therapeutic strategies in the future, will be discussed. A number of case studies will be presented allowing delegates the opportunity to review and test their knowledge and diagnostic skills. An online, interactive forum will be available for discussion of downloadable course material.

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1. Which of the following statements is/are believed to be accurate?

- A) Desmoglein 1 is the principal target auto-antigen in human PF and desmoglein 3 is the principal target auto-antigen in canine PF.
- B) Desmoglein 1 is the principal target auto-antigen in canine PF and desmoglein 3 is the principal target auto-antigen in human PF.
- C) Desmogleins 1 and 3 are major target auto-antigens in both human and canine PF.
- D) None of the above

2. Which of the following drug combinations has/have been described in the literature as having been associated with triggering pemphigus-like signs in dogs?

- A) Metaflumizone and fipronil
- B) Dinotefuran, pyrethrin, permethrin
- C) Fipronil, moxidectin, S-methoprene
- D) Metaflumazone and amitraz

3. Which of the following presentations would be typical of canine PF?

- A) Predilection for head and face
- B) Mucocutaneous distribution
- C) Pedal involvement
- D) All of the above

4. Pair up one phrase from each of the following two groups

- A) Superficial bacterial folliculitis
- B) Canine PF
- C) Human PF
- D) Canine and human PF

- 1) Drugs are possible triggers
- 2) Desmoglein 1 is the major auto-antigen
- 3) One hair typically protrudes through pustule
- 4) Desmoglein 1 is thought to be a minor auto-antigen

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