ISVC Case of the Month April 2021

A one-year four-month old male Basset Hound had a 48 hour-history of an acute onset of vesicles and erosions on the nasal planum (Figure 1A), at the margins of the pads on all four feet (Figure 1B) and the buccal (Figure 2A) and lingual mucosa (Figure 2B). Separation of the pads was observed within 24 hours of onset, accompanied by haemorrhage and purulent exudation. Lethargy, lameness, hypersalivation, anorexia and generalised lymphadenomegaly accompanied the dermatological signs. Recent drug administration was limited to afoxolaner and milbemycin oxime given 21 days before the development of clinical signs. Punch biopsies (6mm) were taken from the nasal planum, buccal mucosa and from the margins of multiple digital pads.

Figure 1

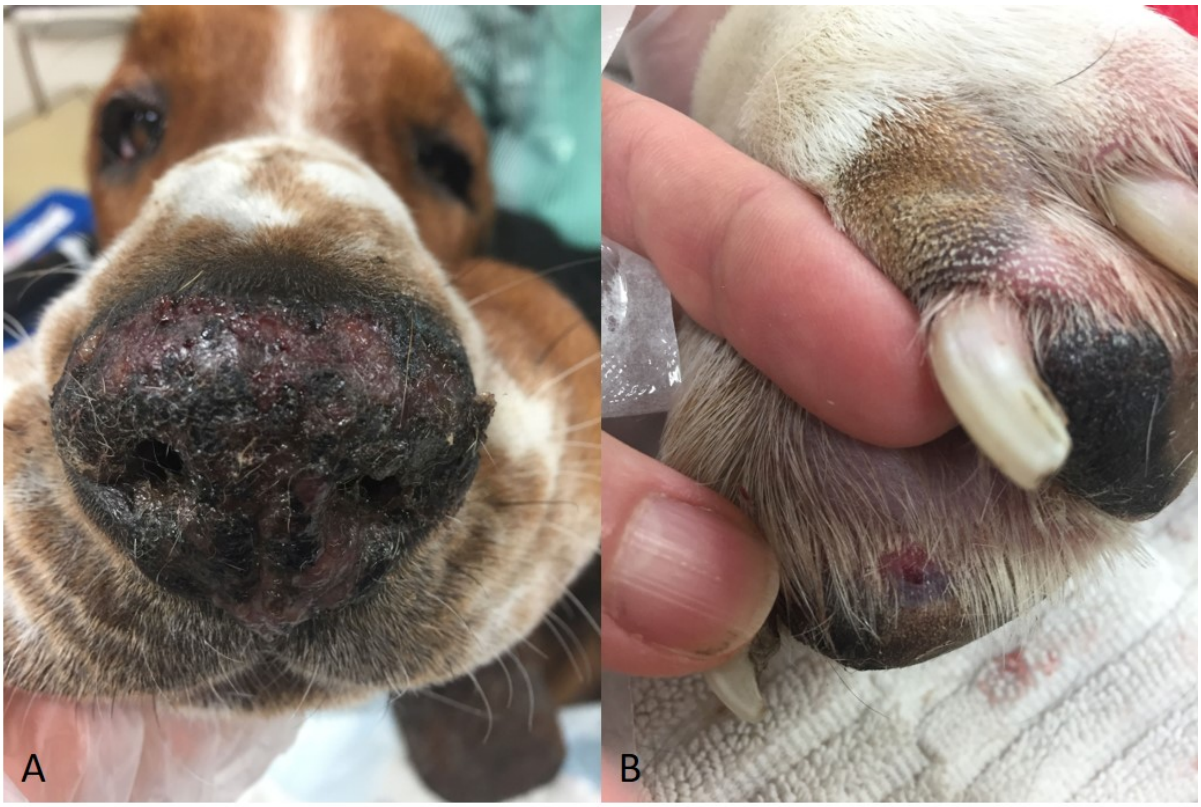


Figure 2.

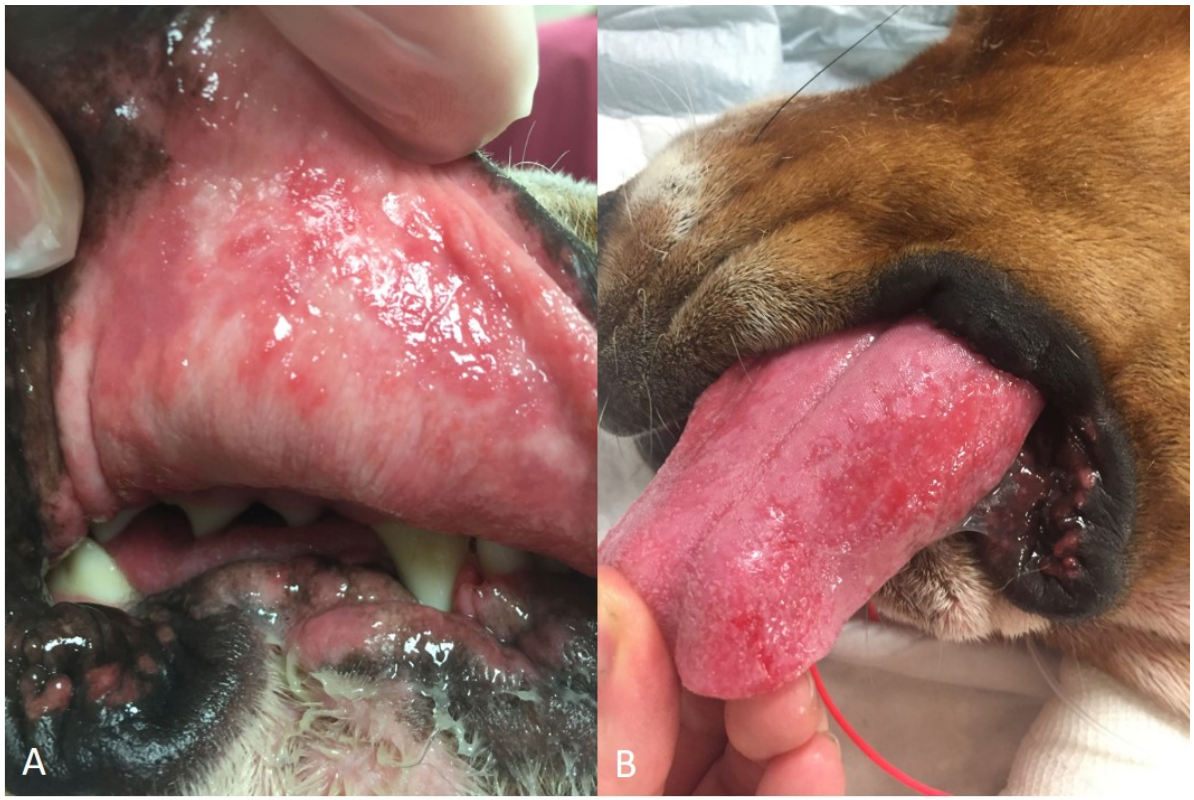
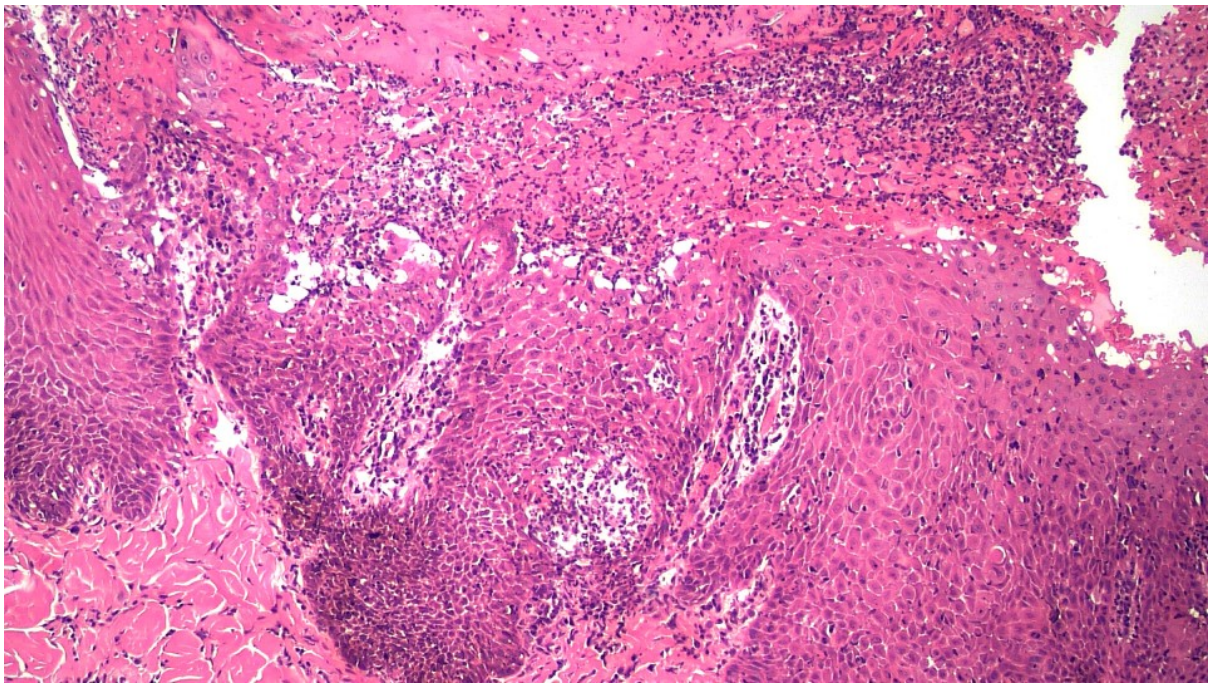


Figure 3.



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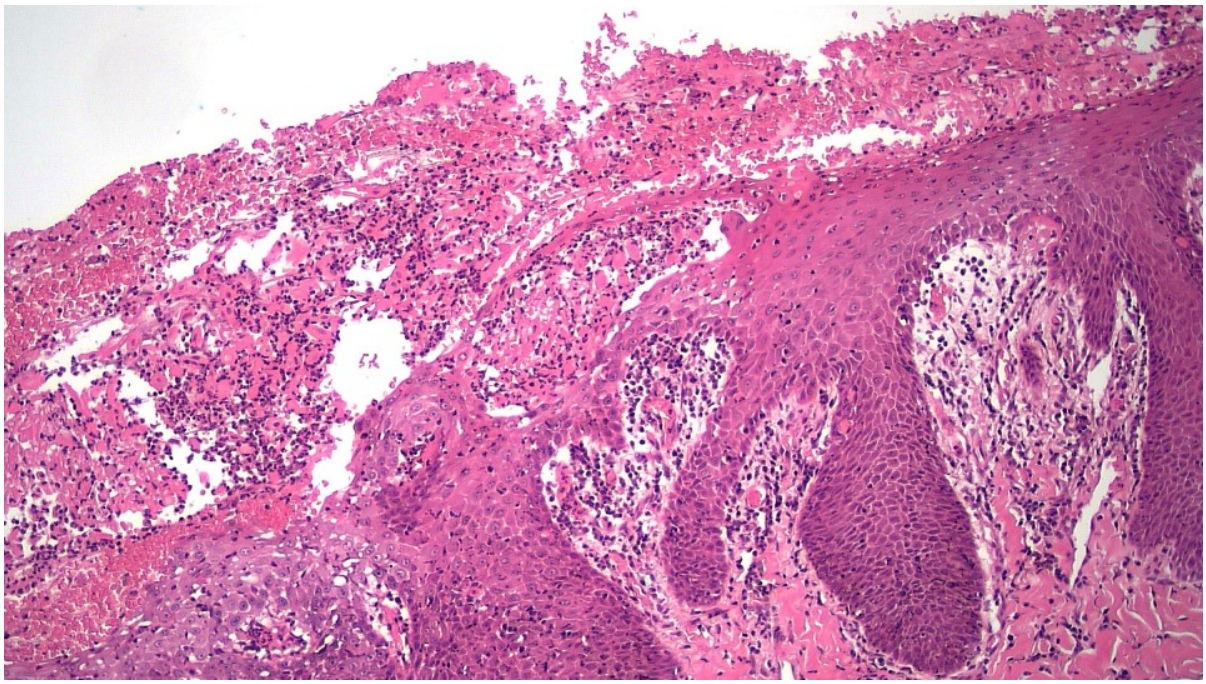

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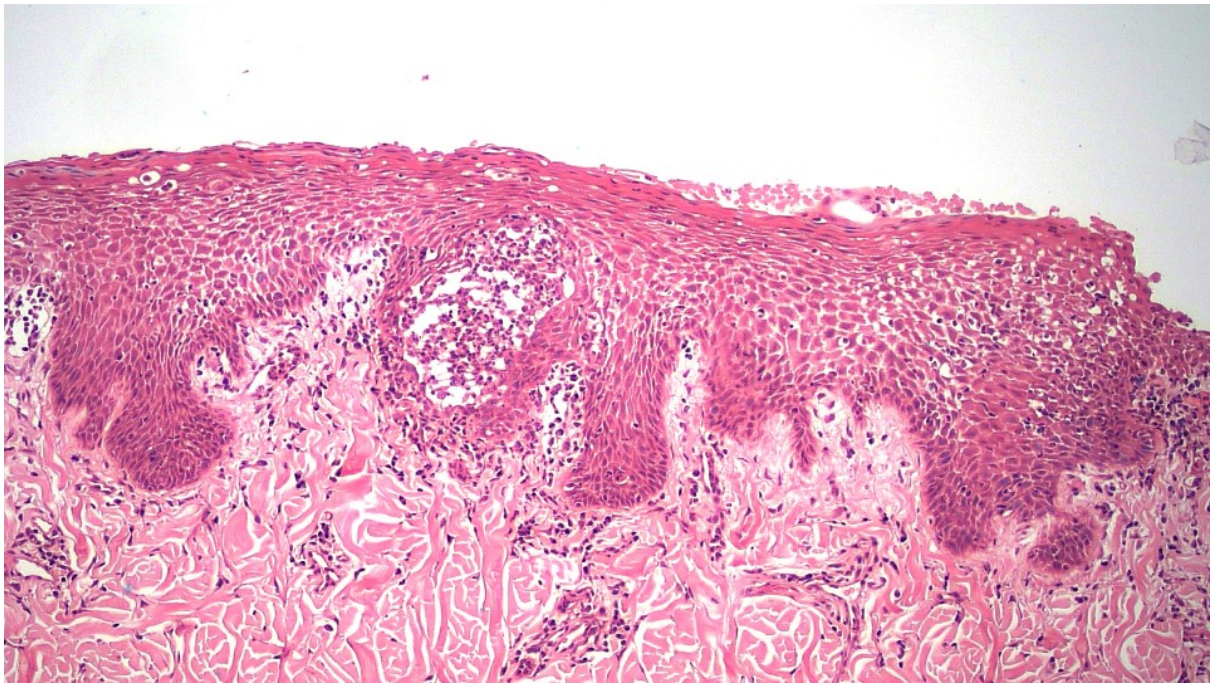

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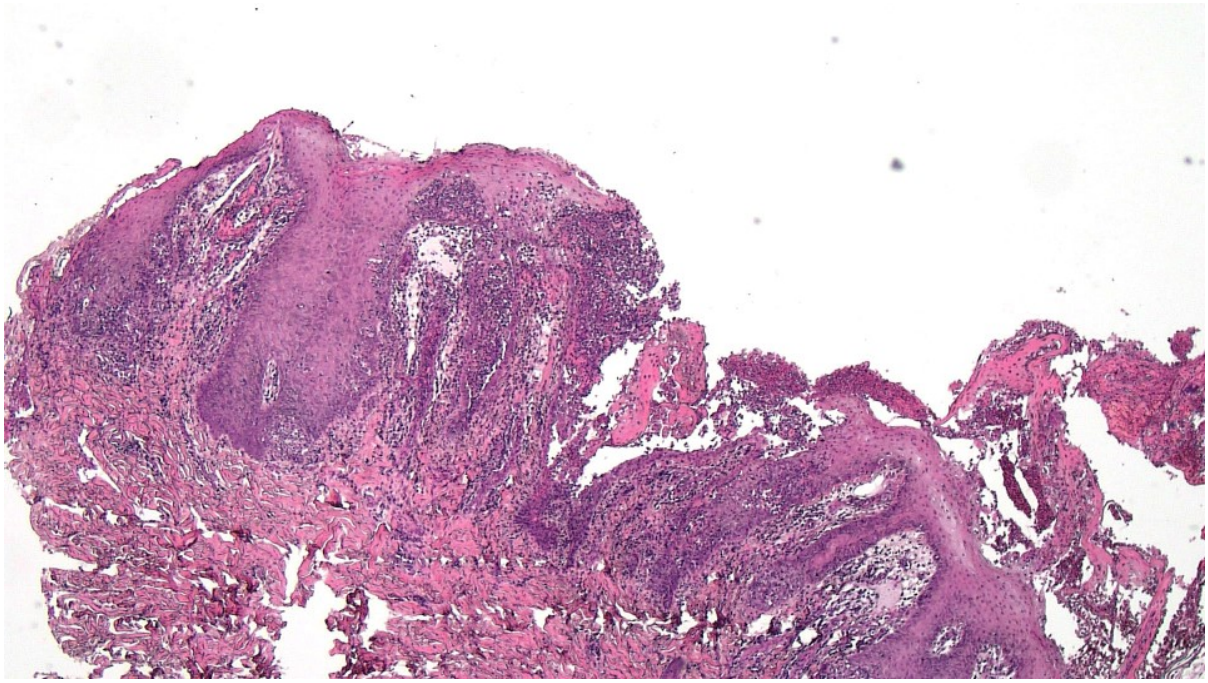

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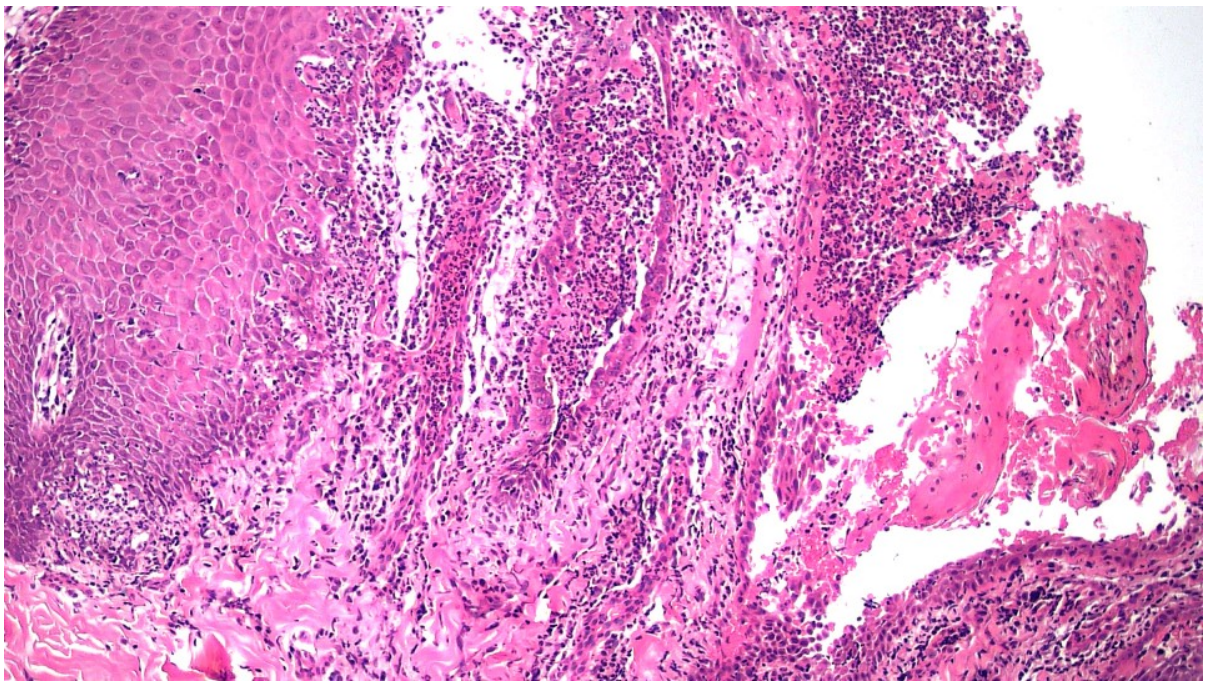
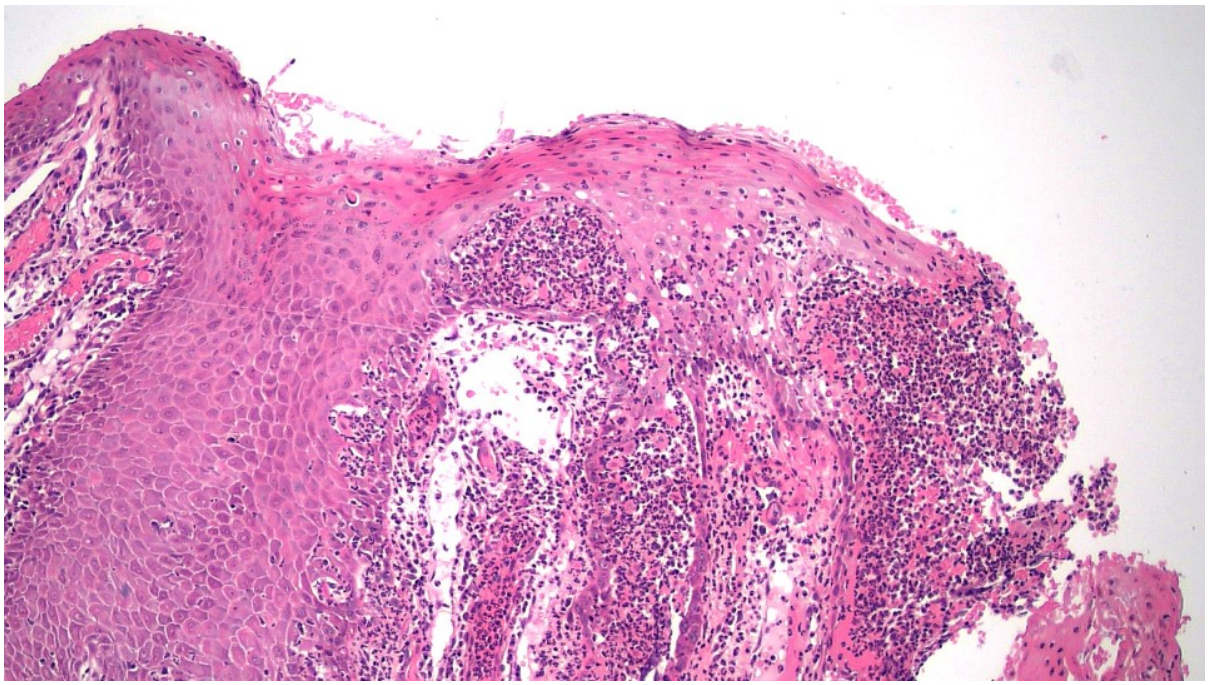


Figure 8.



Which one of the following is the best histopathological diagnosis?

a) Erythema multiforme
b) Pemphigus vulgaris
c) Paraneoplastic pemphigus
d) Pemphigus foliaceus
e) Vesicular cutaneous lupus erythematosus

ANSWER:

Signalment:

One-year four-month old male entire Basset Hound

Clinical History:

This case presented with a 48 hour-history of an acute onset of vesicles and erosions on the nasal planum (Figure 1A), at the margins of the pads on all four feet (Figure 1B) and the buccal (Figure 2A) and lingual mucosa (Figure 2B). Separation of the pads was observed within 24 hours of onset, accompanied by haemorrhage and purulent exudation. Lethargy, lameness, hypersalivation, anorexia and generalised lymphadenomegaly accompanied the dermatological signs. Recent drug administration was limited to afoxolaner and milbemycin oxime given 21 days before the development of clinical signs. Punch biopsies (6mm) were taken from the nasal planum, buccal mucosa and from the margins of multiple digital pads.

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Histopathological description:

Nasal planum (Figures 3 and 4):

Expanding the epidermis is a focally extensive serocellular crust populated by eosinophilic and karyorrhectic debris, degenerate neutrophils, fewer lymphocytes and plasma cells, and colonies of bacterial cocci admixed with individual or rafts of acantholytic keratinocytes (Figure 3). The base of this reaction forms ragged clefts of varying depth lined by more than one layer of keratinocytes, some of which show signs of acantholysis and apoptosis and are surrounded by neutrophils. Adjacent to the clefts, the epidermis is mildly and diffusely hyperplastic forming arborizing rete pegs with prominent spongiosis. Rare individual apoptotic keratinocytes are present throughout all levels of the epidermis. In another section (Figure 4), a large neutrophilic pustule at the level of the spinous layer contains abundant acantholytic cells. A moderate superficial dermal oedema and perivascular lymphoplasmacytic infiltrate is also present.

Buccal mucosa (Figure 5):

Apoptotic keratinocytes are scattered throughout all layers of the hyperplastic and spongiotic epidermis, variably associated with neutrophils. Occasionally discrete neutrophilic pustules are located suprabasally. A mild superficial perivascular lymphoplasmacytic infiltrate and oedema is present.

Pad margins (Figures 6-10):

Similarly, to the nose, an extensive serocellular crust is present that is populated by eosinophilic and karyorrhectic debris, degenerate neutrophils, fewer lymphocytes and plasma cells, and colonies of bacterial cocci admixed with individual or rafts of acantholytic keratinocytes (Figure 6). There is

extensive suprabasilar clefting (Figure 9, white arrows) with the adjacent spinous layer disrupted by either acantholytic erosions or large pustules comprising abundant neutrophils and acantholytic (Figure 10, ovals) and apoptotic keratinocytes (Figure 9 and 10, black arrows). Individual apoptotic keratinocytes are scattered throughout multiple layers of the epidermis, but are primarily seen in the deeper layers. A moderate perivascular lymphoplasmacytic and neutrophilic infiltrate is present in the superficial dermis that occasionally extends to and obscures the dermo-epidermal junction.

Figure 9.

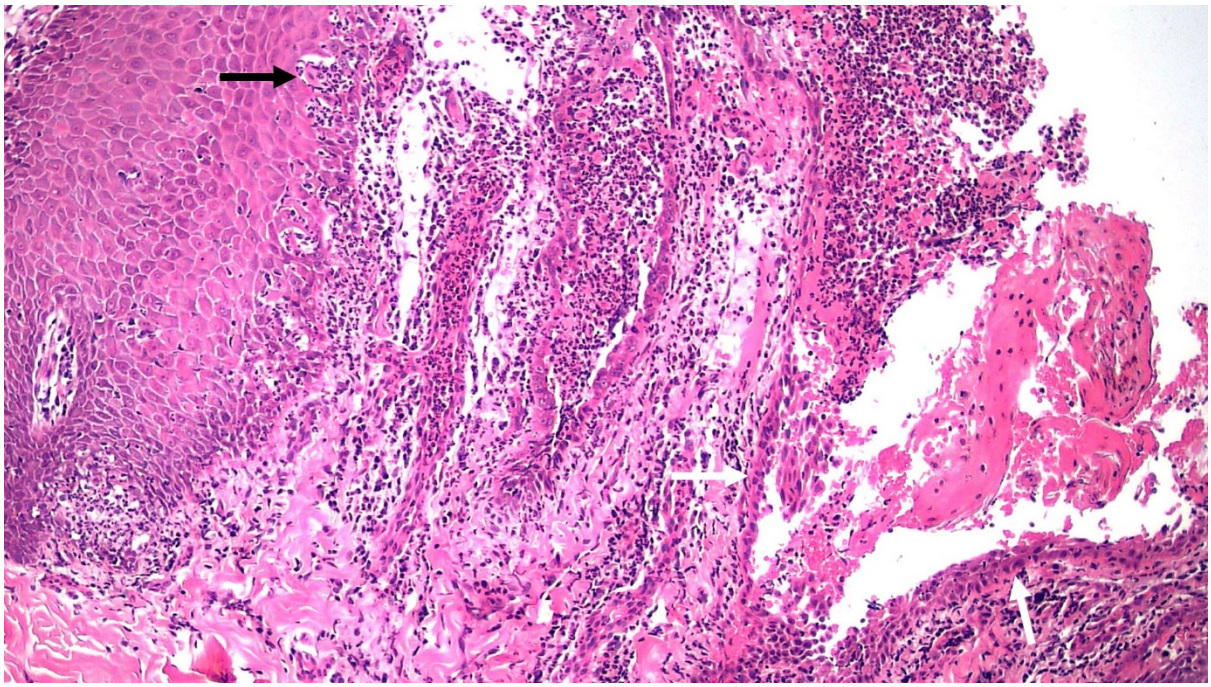
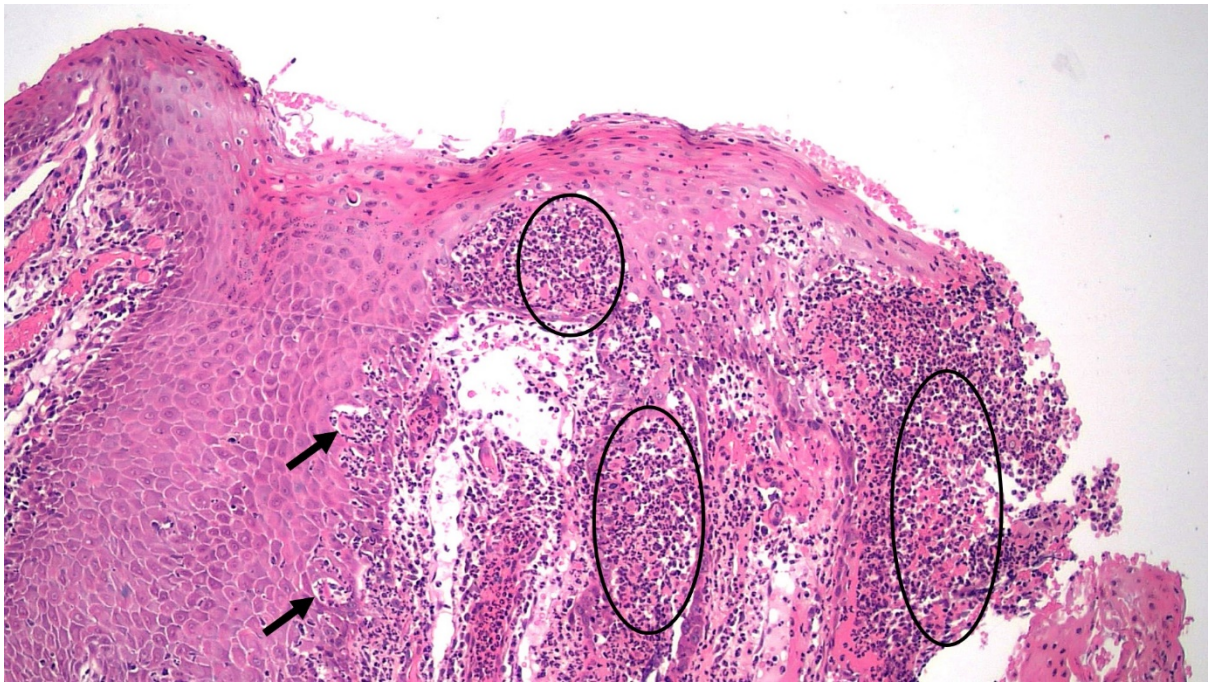


Figure 10.



Morphological diagnosis:

Intraepidermal and intracorneal pustular dermatitis with suprabasilar clefts and keratinocyte acantholysis and apoptosis, marked spongiosis and a perivascular and focal interface lymphoplasmacytic dermatitis.

Comment:

This case of erosive, blistering dermatitis and stomatitis was associated with a highly unusual overlapping constellation of histopathological features more typically observed in several distinct bullous, pustular and acantholytic disorders of dogs. Intraepidermal pustules with free keratinocytes is a typical feature of pemphigus foliaceus, whereas suprabasilar clefting is most often associated with pemphigus vulgaris. Apoptosis at multiple levels in the epidermis is an important feature of erythema multiforme.

Paraneoplastic pemphigus (PNP) is a disease rarely reported in people, very rarely in dogs, and reported in one cat and one horse (Elmore *et al*., 2005; Hill *et* al., 2013; Lemmens *et al*., 1998 and Williams *et al*., 1995). The histological features in this case match textbook descriptions of PNP, comprising an overlap of pemphigus vulgaris (suprabasal acantholysis and clefting), erythema multiforme (apoptosis of keratinocytes in multiple epidermal layers) and pemphigus foliaceus (intra-epidermal pustulation with acantholytic keratinocytes). The degree of apoptosis is not consistent with the pan-epidermal or pan-follicular variant of pemphigus foliaceus (Gross *et al*., 2008, Kimyai-Asadi and Jih 2001). From a comparative aspect, human pemphigus vegetans is associated with eosinophilic pustules, and human benign familial chronic pemphigus (the 'crumbling brick wall') lacks the granulocytic pustules.

Evidence for a diagnosis of PNP in this case could have strengthened by performing indirect immunofluorescence and immunoprecipitation to establish if antibodies targeting both epidermal plakins and desmoglein-3 were present (de Bruin *et al*. 1999).

Since the few case reports of PNP in non-human species have mostly been associated with an underlying neoplastic process, further investigations in this patient consisted of a full body CT scan, haematology, biochemistry, urinalysis and fine needle aspiration of the enlarged lymph nodes. No evidence of neoplasia was found, however, since PNP can precede signs of neoplasia in people, an underlying neoplasia could not be completely ruled out in this case, but is less likely due to the patient's age (Kimyai-Asadi and Jih 2001). Human PNP is typically refractory to immunosuppressive therapy and successful treatment is reliant on identification and resolution of the underlying neoplasia (Kimyai-Asadi and Jih 2001). This case responded rapidly to treatment with 2mg/kg prednisolone and treatment was successfully withdrawn over the following two months without relapsing disease at the time of writing (six months after cessation of therapy).

Whilst there are no published case reports of PNP in dogs without neoplasia, Gross *et al.* (2008) and Maudlin and Peters-Kennedy (2016) note that not all cases with characteristic histological and or clinical signs of PNP, including the above autoantibodies, have an underlying neoplastic process and signs may even be transient suggesting there are alternative triggers to this reaction pattern. In this case, it is most likely that neoplasia was not the inciting cause. Furthermore, the drug history was not overtly compatible with an adverse drug reaction as the combined tablet of afoxolaner and milbemycin oxime was given 21 days beforehand and several times prior to this. Afoxolaner has been reported as a suspected idiosyncratic trigger of pemphigus foliaceus in a dog although with more rapid onset of initial signs reported, within seven days of first dosing, than in this case (White

et al. 2019). Thus, whilst the histopathological features most closely resemble PNP, the final clinical diagnosis, and inciting trigger(s), remain uncertain.

References:

de Bruin A, Müller E, Wyder M, Anhalt GJ, Lemmens P, Suter MM. Periplakin and envoplakin are target antigens in canine and human paraneoplastic pemphigus. J Am Acad Dermatol [Internet]. 1999;40(5):682–5. Available from: http://www.sciencedirect.com/science/article/pii/S0190962299701477

Elmore SA, Basseches J, Anhalt GJ, Cullen JM, Olivry T. Paraneoplastic pemphigus in a dog with splenic sarcoma. Vet Pathol. 2005 Jan;42(1):88–91.

Gross TL, Ihrke PJ, Walder EJ, Affolter VK. Bullous and Acantholytic Diseases of the Epidermis and the Dermal-Epidermal Junction. In: Skin Diseases of the Dog and Cat. John Wiley & Sons, Ltd; 2008. p. 36-38. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9780470752487.ch2

Hill PB, Brain P, Collins D, Fearnside S, Olivry T. Putative paraneoplastic pemphigus and myasthenia gravis in a cat with a lymphocytic thymoma. Vet Dermatol. 2013 Dec;24(6).

Kimyai-Asadi A, Jih MH. Paraneoplastic pemphigus. Int J Dermatol. 2001;40(6):367-372. doi:10.1046/j.1365-4362.2001.01169.x

Lemmens, Bruin D, Meulemeester D, Wyder, Suter. Paraneoplastic pemphigus in a dog. Vet Dermatol [Internet]. 1998;9(2):127–34. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-3164.1998.00095.x

Mauldin EA, Peters-Kennedy J. Chapter 6 - Integumentary System. In: Maxie MG, editor. Jubb, Kennedy & Palmer's Pathology of Domestic Animals: Volume 1 (Sixth Edition) [Internet]. W.B. Saunders; 2016. p.603. Available from: http://www.sciencedirect.com/science/article/pii/B9780702053177000060

Williams MA, Dowling PM, Angarano DW, et al. Paraneoplastic bullous stomatitis in a horse. J Am Vet Med Assoc. 1995;207(3):331-334.

Contributors:

Clinical management:

Sarah Long, Resident in Veterinary Dermatology, Royal Veterinary College

Ross Bond, Professor of Veterinary Dermatology, Royal Veterinary College

Clinical images kindly provided by Johann Boone, Resident in Veterinary Dermatology, Royal Veterinary College

Histopathology:

Gordon Davidson, Resident in Veterinary Anatomic Pathology, Royal Veterinary College

Henny Martineau, Senior Lecturer in Veterinary Anatomic Pathology, Royal Veterinary College