Successful long-term management of mucocutaneous pemphigus vulgaris with oral ciclosporin and vitamin E in a dog

Dayle McClintock1,*, Frane Banovic1, Pauline Rakich2, Michaela Austel1

1) Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, 2200 College Station Road, Athens, GA, 30605, USA, 2) Department of Pathology, College of Veterinary Medicine, University of Georgia, 501 D.W. Brooks Drive, Athens, GA, 30602, USA

Received October 13, 2020 and accepted January 28, 2021

Abstract: A 10-year-old, male neutered Husky-mix had clinical and histopathological findings consistent with mucocutaneous pemphigus vulgaris. After steroid induction, the patient remained in remission with two minor relapses with ciclosporin and vitamin E for 23 months. To the best of the authors’ knowledge, this is the first report of long-term control of canine pemphigus vulgaris with ciclosporin and vitamin E.

Key words: ciclosporin, pemphigus vulgaris

Introduction

Canine pemphigus vulgaris (PV) is a very rare autoimmune disease driven by autoantibodies directed at intercellular adhesion proteins of keratinocytes, most pervasively desmoglein-3, resulting in loss of keratinocyte adhesion5, 7). Therapeutic management of canine PV typically requires immunosuppression, initially with oral glucocorticoids prescribed at high dosages9). Nonsteroidal agents to manage canine PV have historically included vitamin E, niacinamide, doxycycline, aurothioglucose, chlorambucil, and azathioprine, with some combinations leading to partial or complete remission3, 9). However, there is still a reported 40% euthanasia rate due to undesirable treatment side effects or failure in canine patients2, 8). Ciclosporin, a potent calcineurin inhibitor, inhibits the activation of T-helper cells and decreases the synthesis of inflammatory cytokines, but has previously not been shown to be effective as a sole agent for autoimmune diseases such as pemphigus foliaceus1, 9). This case report details the successful long-term control of a dog with canine PV treated with oral ciclosporin and vitamin E following induction of remission with oral glucocorticoids.
Case Report

A 10-year-old, 24 kg, castrated male Husky-mix dog was evaluated for a two-month history of sudden-onset, ulcerative skin and oral cavity lesions accompanied by inappetence and lethargy. The lesions were minimally responsive to oral prednisone administered for 7 days (0.5 mg/kg, once daily; Lloyd, Shenandoah, IA, USA). Prednisone was discontinued and the patient was referred one month later to a dermatologist for a biopsy. Upon presentation, the patient exhibited multifocal crusting erosions and ulcerations affecting the concave aspects of the pinnae, the dorsal and ventral neck as well as the left shoulder and thorax. Multiple small ulcerations (1–4 mm in diameter) were noted on the hard palate, the tongue and the lips. Numerous thick-walled vesicles covered the lips and buccal mucosa (Fig. 1). Cytology from a vesicle on the lip consisted of neutrophils mixed with a moderate number of acantholytic keratinocytes. No microbial organisms were observed despite extensive searching. Clinical differentials for the lesions included pemphigus vulgaris, mucous membrane pemphigoid, bullous pemphigoid, epidermolysis bullosa acquisita, and paraneoplastic pemphigus.

A total of four 8-mm punch biopsies were collected from the lip, neck, and shoulder. Histopathological evaluation revealed hyperplastic superficial perivascular to diffuse interstitial and periadnexal dermatitis with suprabasilar and intraepidermal clefting and marked serocellular crusting (Fig. 2); rare individual keratinocyte cell death was observed only in the lip section. The history, clinical features, and histopathology were most consistent with a diagnosis of pemphigus vulgaris (PV). The main histopathological differential diagnosis was canine paraneoplastic pemphigus (PNP). The owner elected to pursue immunosuppressive therapy for autoimmune disease and declined diagnostic testing to evaluate the patient for underlying neoplastic disease.

Treatment was initiated with oral dexamethasone (0.1 mg/kg, once daily; Boehringer Ingelheim, Columbus, OH, USA) and topical betamethasone dipropionate cream (0.05%, twice daily; Merck, Whitehouse Station, NJ, USA). Seven days later, oral ciclosporin was added (2 mg/kg, once daily for 7 days, then 4 mg/kg, once

Fig. 1. Clinical pictures of canine mucocutaneous pemphigus vulgaris. (a–b) Patient lesions present at time of biopsy showing thick walled mucosal vesiculation and pinnal erosions. (c–d) Patient after fifteen months on ciclosporin with lesions in remission.
daily thereafter; Atopica, Elanco, Greenfield, IN, USA) and the dexamethasone dose increased (0.2 mg/kg, once daily). Complete clinical resolution was achieved within 6 weeks, at which time oral and topical steroids were gradually tapered and discontinued. Oral vitamin E (800 IU, once daily; Nature Made, West Hills, CA, USA) was added as had been prescribed in previous cases\(^7\), and the patient was switched to a generic formulation of oral ciclosporin (4 mg/kg, once daily; Teva, North Wales, PA, USA). Remission was maintained for three months without dose adjustment. Attempts to decrease ciclosporin dosing frequency in the following months led to two relapses with mild pinnal erosions and crusting. Relapses occurred when ciclosporin administration frequency was decreased from once daily to every other day. Remission in each episode was achieved by increasing ciclosporin back to once daily and applying betamethasone dipropionate cream to active lesions.

Thirteen months following initial clinical remission, the oral ciclosporin dose was able to be reduced to 4 mg/kg every other day without relapse. Fifteen months following clinical remission, ciclosporin was reduced to 4 mg/kg twice weekly, and the patient remained in remission for 8 months until his death due to cardiac and splenic hemangiosarcoma. There were no skin or oral cavity lesions at the time of his death.

**Discussion**

To the authors’ knowledge, this is the first reported case of long-term control of canine PV with ciclosporin and vitamin E following initial induction of remission using glucocorticoids. This is in contrast to reported failure of ciclosporin as a single agent therapy for a similar canine pemphigoid disease, pemphigus foliaceus, and in contrast to reported failure of other steroid-sparing agents to control canine PV outcomes that often have more severe side effects\(^2,6\). In humans, PV is more common than in dogs, but severe ciclosporin side effects and failure to control the disease largely preclude its use\(^11\). Prior to the case reported here, a dosage of ciclosporin for management of canine PV has been proposed at 5–10 mg/kg/day, based on authors’ personal experiences and extrapolation from management of other canine autoimmune diseases\(^1,9\). The only other case reports of ciclosporin being used as a steroid-sparing agent in dogs used significantly higher doses of a human product (10-25 mg/kg/day, Sandimmun\(^\text{®}\), Sandoz, now Novartis, Nuernberg, Germany) which achieved remission from 6 weeks to 9 months in three patients\(^10\). This is in contrast to the case reported herein where a veterinary product effectively maintained remission at a significantly lower dose. Side effects of ciclosporin most commonly include vomiting and diarrhea, which can be a reason for decreasing or stopping therapy\(^5\). The dose in this case report was below that range due to capsule size limitation but proved effective and the patient...
experienced none of these side effects. As reported herein, attempts to reduce the dosing frequency to less than daily after less than a year on ciclosporin led to two relapses. The significance of the ability to taper the dose after the first thirteen months of therapy is not known at this point in time. Administration of ciclosporin to future cases of canine PV may help better determine the safest course for tapering the medication in these patients.

The primary histopathological differential diagnosis for our canine PV case was paraneoplastic pemphigus (PNP), another rarely reported autoimmune mucosal and mucocutaneous subcorneal blistering disease that also presents with suprabasilar clefting as seen in PV\(^4\). Immunohistochemistry (IHC) can be used to highlight distribution of autoreactive antibodies targeting intercellular proteins in the affected tissues\(^9\), in order to help differentiate cases of PNP and PV which are not clinically differentiated. Canine PNP autoantibodies are frequently polyclonal, targeting periplakin and envoplakin in addition to desmoglein-3\(^6,8\). The client in this case declined further diagnostics, including IHC and screening for neoplasia at the time of histopathological diagnosis. Despite his eventual death from splenic and cardiac hemangiosarcoma, this patient lived over two years following diagnosis of canine PV while undergoing immunosuppressive therapy and had no mucosal or cutaneous lesions at the time of his death. In contrast, canine PNP patients typically die or are euthanized within weeks of diagnosis due to neoplasia and persistent skin lesions\(^5,8\), making canine PNP an unlikely diagnosis for the case reported herein.

To the best of the author’s knowledge, this is the first report of long-term control of canine PV using lower than previously reported doses for ciclosporin and vitamin E, making it a valid therapeutic option for these patients.

**Conflicts of Interest:** No authors have any conflicts of interest.

**References**

1) Archer, T.M., Boothe, D.M., Langston, V.C., Fellman, C.L., Lunsford, K.V. and Mackin, A.J. 2014. *J. Vet. Intern. Med.* 28: 1–20.
2) Blair, R.V., Wakamatsu, N. and Pucheu-Haston, C.M. 2015. *J. Am. Vet. Med. Assoc.* 246: 419–421.
3) Foster, A.P. and Olivry, T. 2001. *Vet. Rec.* 148: 450–451.
4) Gross, T.L., Ihrke, P.J., Walder, E.J. and Affolter, V.K. 2005. pp. 32–40. *In: Skin diseases of the dog and cat: clinical and histopathologic diagnosis* second edition (Gross, T.L. and Ihrke, P.J., eds.), Blackwell Science Ltd, Iowa.
5) Nishifuji, K., Olivry, T., Ishii, K., Iwasaki, T. and Amagai, M. 2007. *Vet. Immunol. Immunopathol.* 117: 209–221.
6) Olivry T.2003. pp. 263–273. *In: Animal Models of Human Diseases* (Chan, L.S. ed.), CRC Press, Washington, D.C.
7) Olivry, T., Joubeh, S., Dunston, S.M., Nishiyama, T. and Ghohestani, R.F. 2003. *Exp. Dermatol.* 12: 198–203.
8) Olivry, T. and Linder, K.E. 2009. *Vet. Dermatol.* 20: 313–326.
9) Rosenkrantz W.S. 2004. *Vet. Dermatol.* 15: 90–98.
10) Zetner, V.K. and Gaspar, A.G. 1987. *Praktishche Tierzart.* 191: 1121–1124.
11) Zhao, C.Y. and Murrell, D.F. 2015. *Drugs.* 75: 271–284.