Ciclosporin induced psoriasiform-lichenoid dermatosis, footpad hyperkeratosis and gingival hyperplasia in a West Highland white terrier dog

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CASE REPORT

Companion or pet animals

Ciclosporin-induced psoriasiform-lichenoid dermatosis, footpad hyperkeratosis and gingival hyperplasia in a West Highland white terrier dog

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Abstract

A 6-year-old male neutered West Highland white terrier presented with gingival hyperplasia and footpad hyperkeratosis 5 months after starting 5 mg/kg ciclosporin once daily. Following cessation of this therapy, the footpad lesions were resolved, while the gingival hyperplasia remained. Two weeks following the re-introduction of ciclosporin, multiple raised, focal crusted papules and plaques along the dorsum, flanks and lateral aspect of all limbs were evident. The dog also developed footpad hyperkeratosis. Punch biopsies of the skin from these lesions confirmed psoriasiform-lichenoid dermatosis. Cessation of the ciclosporin therapy allowed resolution of the nodules within 4 weeks. Haematological and biochemical analyses to assess for systemic disease and to investigate liver function were normal. Gingival hyperplasia was still present 4 weeks after stopping therapy. To the best of the authors' knowledge, this is the first report of a dog presented with multiple rare ciclosporin-induced adverse effects, psoriasiform-lichenoid dermatosis, footpad hyperkeratosis and gingival hyperplasia.

KEYWORDS

ciclosporin, dermatology, dermatopathology

BACKGROUND

Ciclosporin, a calcineurin T-cell inhibitor, is an immunomodulating medication used to treat canine atopic dermatitis (AD) by reducing pruritus and clinical lesions.[1] A wide variety of adverse effects are associated with its use; most commonly noted are gastrointestinal-related signs, which occur in 20%–30% of patients.[2] Other adverse effects appear to be uncommon, and to date, no reports exist of a dog having multiple of these uncommon adverse effects associated with ciclosporin use.

Ciclosporin-associated, and spontaneous, non-ciclosporin-related psoriasiform-lichenoid dermatosis has been reported in dogs.[3,4] The spontaneous form, occurring most notably in the springer spaniel, indicates that a genetic factor is involved. It is considered a rare skin disease that may be associated with a reaction to superficial staphylococcal infection, likely due to an aberrant immunological response.[5] In humans with psoriasis, it may also be associated with the production of superantigens that trigger the local skin reaction.[6] The true incidence of this is unknown; however, psoriasiform-lichenoid dermatosis was identified in 1% of dogs on ciclosporin in one report,[1] with papillomavirus detected in some cases.[5]

The reported incidence rate of gingival hyperplasia in dogs treated with ciclosporin is 2%–3% and is not concentration-related, as dogs on a standard dose of 5 mg/kg can develop these lesions. It is mostly cosmetic but can cause the formation of deep gingival pockets, thus predisposing to the development of dental disease.[7] The exact mechanism is not fully understood.

In addition, footpad hyperkeratosis has also been rarely reported as callus-like lesions on the footpads of dogs and appears mostly associated with doses above the reference range in clinical trials (Cyclavance, Virbac). All of these proliferative-type lesions described above are benign, should not cause any significant ill effect to the patient and should regress upon stopping ciclosporin.[1] While these adverse effects are reported, there has been no such report of any dog having combinations of these adverse effects concurrently. We report a case of a dog on systemic ciclosporin therapy, with multiple adverse effects of systemic ciclosporin therapy; psoriasiform-lichenoid dermatosis; gingival hyperplasia and footpad hyperkeratosis.

CASE PRESENTATION

Two years ago, a 4-year-old male neutered West Highland white terrier was presented for investigation of pruritic skin disease and was diagnosed with AD.[8] A congenital extrahepatic portosystemic shunt (PSS) was also diagnosed at the same time and surgically repaired by ligation. All blood abnormalities and clinical signs associated with this were resolved after surgery.

Following the diagnosis of AD, treatment was initiated with prednisolone 0.5–1 mg/kg once daily, subcutaneous allergen-specific immunotherapy injections for 12 months and more recently intralymphatic immunotherapy injections.

Immunotherapy was not considered beneficial and was stopped. Courses of both oclacitinib (Apoquel Zoetis) and lokivetmab (Cytopoint, Zoetis) had been partially successful in reducing pruritus, but the inflammation continued to progress, and the dog required a regular course of prednisolone to control it.

The dog was started on ciclosporin (Cyclavance, Virbac) at 5 mg/kg orally once daily for 5 months, which improved pruritus and clinical lesions; however, the dog developed footpad hyperkeratosis (Figure 1a) and mild gingival hyperplasia (Figure 1b); thus, ciclosporin was stopped.

This is an example of a case refractory to the conventional AD treatment, and therefore the addition of alternative immunomodulatory therapies had to be considered. After discussing the options with the owner, we opted for the off-licence use of chlorambucil due to its steroid-sparing effect but also because it was considered a safer agent due to the fewer concerns regarding hepatotoxicity (compared to other immunosuppressive/immunomodulatory drugs).[9] Idiosyncratic hepatotoxicity rarely occurs in humans on chlorambucil, and only occasional reports in dogs exist.[10] Chlorambucil (Leukeran; Aspen) at 0.2 mg/kg once daily and topical therapy of hydrocortisone aceponate (Cortavance; Virbac) and chlorhexidine/miconazole shampoo (Malaseb; Dechra) was initiated to replace the systemic effects of ciclosporin. Additional prednisolone 1 mg/kg once daily was used for 10 days combined with the above topical therapy for a flare of superficial pyoderma in which methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) was isolated.

Since 3 months of chlorambucil did not produce any appreciable benefits to the dog's pruritus and clinical lesions, this therapy was stopped, and ciclosporin was re-introduced at 5 mg/kg once daily since a good response was achieved last time it was used. Two weeks after re-starting ciclosporin, the dog presented with multiple, well-demarcated focal areas of crusted papules and plaques, some of which were coalescing along the dorsum, top of the head and lateral limbs (Figure 2a–c). Gingival hyperplasia was still present and unchanged (Figure 2d), and there was no return of the footpad hyperkeratosis, although marked 'false-pad' formation and chronic pododermatitis were present (Figure 2e). Cytology from the affected areas of crusted plaques showed low numbers of degenerate neutrophils with a moderate number of bacteria (cocci) and normal non-nucleated keratinocytes. The dog was sedated for collection of three, 6 mm skin punch biopsy samples from the raised plaque-like lesions into 10% formalin and sent for routine histopathology. Ciclosporin was again stopped at the time of biopsy, and no systemic therapy was given until the histopathology results were available.

LEARNING POINTS/TAKE HOME MESSAGES

- Psoriasiform-lichenoid dermatosis, footpad hyperkeratosis and gingival hyperplasia are all rare adverse effects associated with systemic ciclosporin that vets need to be aware of.
- These side effects can occur concurrently and most likely will resolve after medication withdrawal if they are diagnosed on time.

INVESTIGATIONS

Haematology and serum biochemistry showed non-significant mildly elevated globulin 42.2 g/L (reference range 18–37 g/L), AP 77 U/L (reference range 20–60 U/L), glucose 7.1 mmol/L (3–5 mmol/L), and a mildly reduced alanine aminotransferase (ALT) 15 U/L (reference range 21–102 U/L). Due to the previous PSS history and a possibility of reduced liver metabolism of ciclosporin causing the adverse effects, a fresh heparinised sample for ammonia was assessed and was within normal limits of 9 umol/L (reference range 0–98 umol/L). Hepatic function was considered normal and not assessed further.

The histopathological findings of lymphocytic-plasmacytic infiltrate in the superficial dermis, irregular acanthosis and parakeratosis of the epidermis, and marked serocellular crusting and eosinophilic intracorneal pustules confirmed the diagnosis of psoriasiform-lichenoid dermatosis (Figure 3).

DIFFERENTIAL DIAGNOSIS

Psoriasiform-lichenoid-like dermatitis, bacterial infection, fungal infection, dermatophytosis, papillomatosis, epitheliotropic T-cell lymphoma were the differential diagnoses.

OUTCOME AND FOLLOW-UP

The psoriasiform-lichenoid dermatosis was resolving at Day 14, with the hyperkeratotic plaques giving the appearance of disintegrating (Figure 4a) and had fully resolved by Day 28 after stopping systemic ciclosporin (Figure 4b), with only a mild residual scale present (Figure 4c). The dog was MRSP culture-negative by day 45 after stopping ciclosporin therapy. The footpad hyperkeratosis resolved after the first time ciclosporin was stopped and did not return, while the gingival hyperplasia remained stable throughout (Figure 4d; see supporting information for the timeline)

DISCUSSION

This report describes a case of presumed ciclosporin-induced psoriasiform-lichenoid dermatosis with concurrent gingival hyperplasia and footpad hyperkeratosis in a dog. The psoriasiform-lichenoid dermatosis was confirmed by

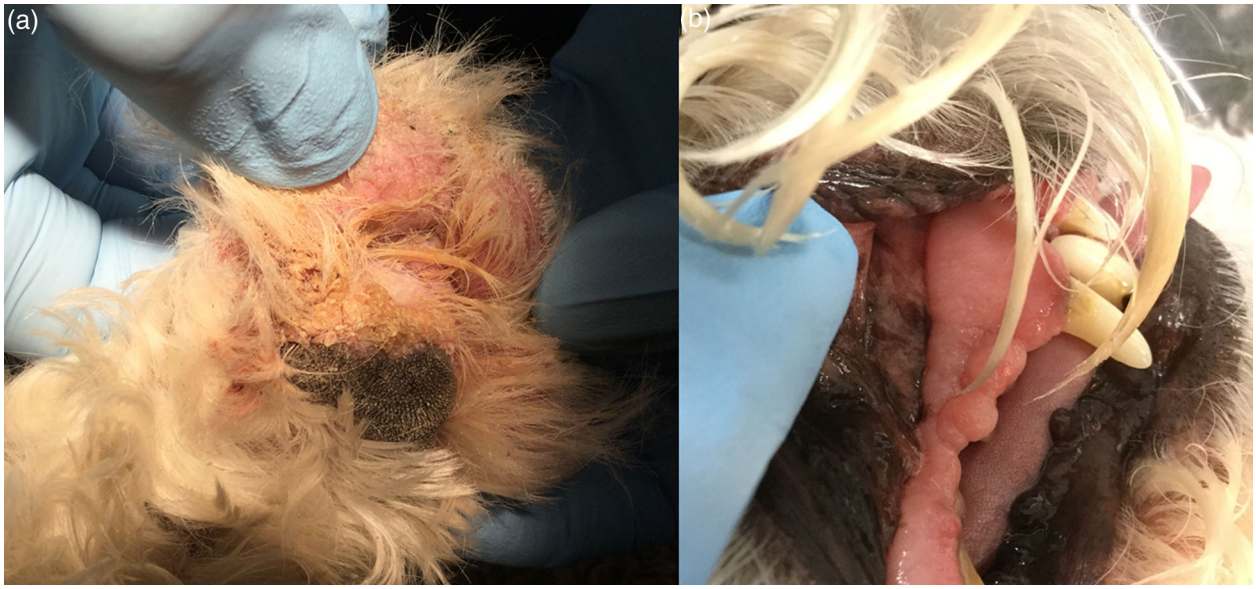

FIGURE 1 Ciclosporin-induced side effects on a West Highland white terrier dog after 5-month therapy with ciclosporin 5 mg/kg once daily: (a) Footpad hyperkeratosis with all four paws similarly affected, and (b) gingival hyperplasia affecting mainly maxillary teeth

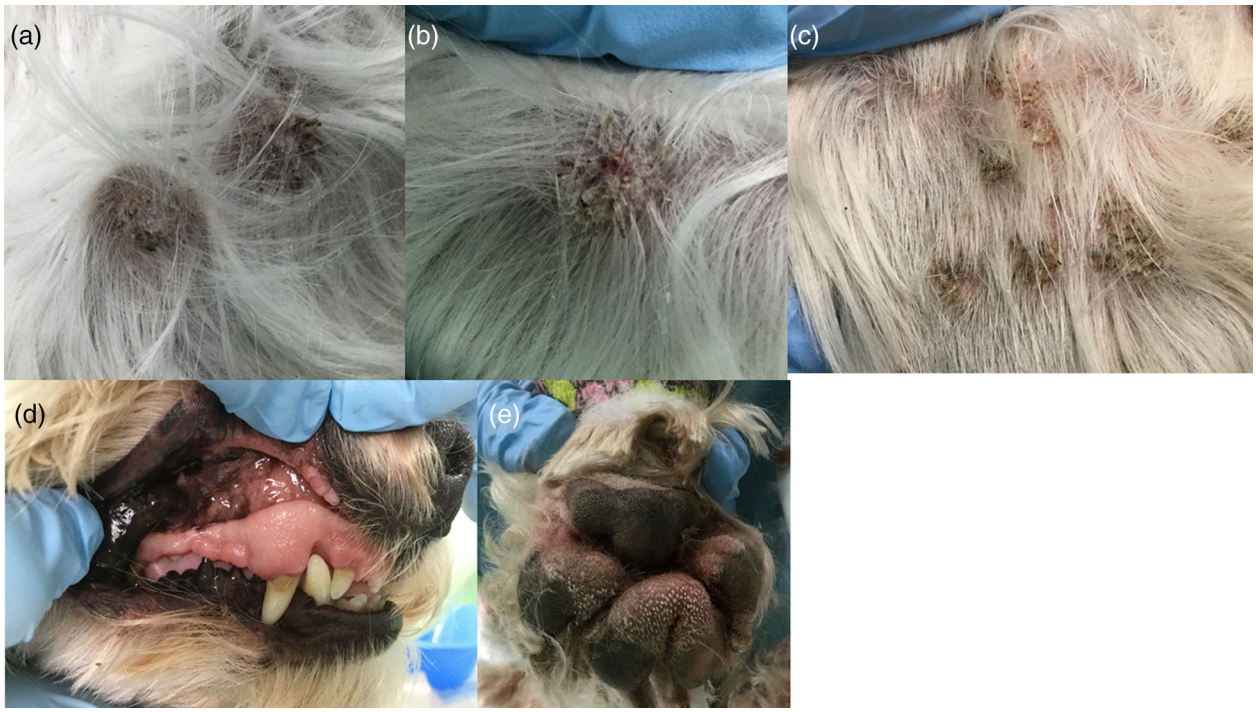

FIGURE 2 Clinical presentation of a West Highland white terrier dog 2 weeks after re-starting ciclosporin on 5 mg/kg once daily. (a–c) Crusted papules and plaques along the dorsum, top of the head and lateral limbs compatible with psoriasiform-lichenoid dermatosis on histopathology findings; (d) Gingival hyperplasia remained stable; (e) resolution of previously diagnosed footpad hyperkeratosis and 'false pad' formation present

histopathology and resolved following the withdrawal of the ciclosporin. Previously documented cases of this condition have not had the gingival hyperplasia or footpad hyperkeratosis components. An additional and non-significant adverse effect of ciclosporin was a mild reduction in ALT, which is reported in 2.6% of cases.[1] This is, therefore, the first case in a dog with multiple, uncommon adverse effects associated with ciclosporin therapy.

Of note, in this case, was the rapid onset of clinical lesions of psoriasiform-lichenoid dermatosis, only 2 weeks after starting the standard dose of ciclosporin. Dogs were previously reported to develop these lesions after 9 weeks, 8 months and 2 years after starting ciclosporin therapy.[3]

Ciclosporin-associated psoriasiform-lichenoid dermatosis is identical to the lesions reported in springer spaniels and is postulated to be related to an exaggerated reaction to staphylococcal infection. In this case, the dog was MRSP-positive at the time of the lesions, although only low numbers of bacteria (cocci) were noted on cytology. At the previous visit, the dog had a significant superficial pyoderma (when the MRSP was initially identified), which was then treated with topical antimicrobial agents. Some dogs with

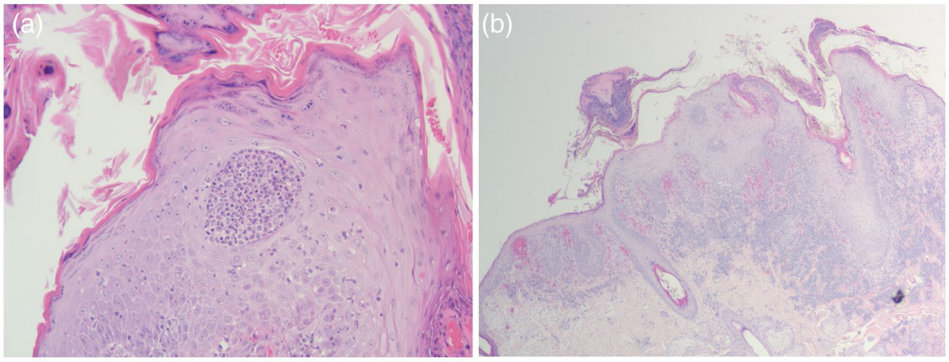

FIGURE 3 Histopathological findings in a West Highland white terrier with ciclosporin-induced psoriasiform-lichenoid dermatosis. (a) Intraepidermal pustule, and (b) thick subepidermal inflammation band showing epidermal hyperplasia and hyperkeratosis

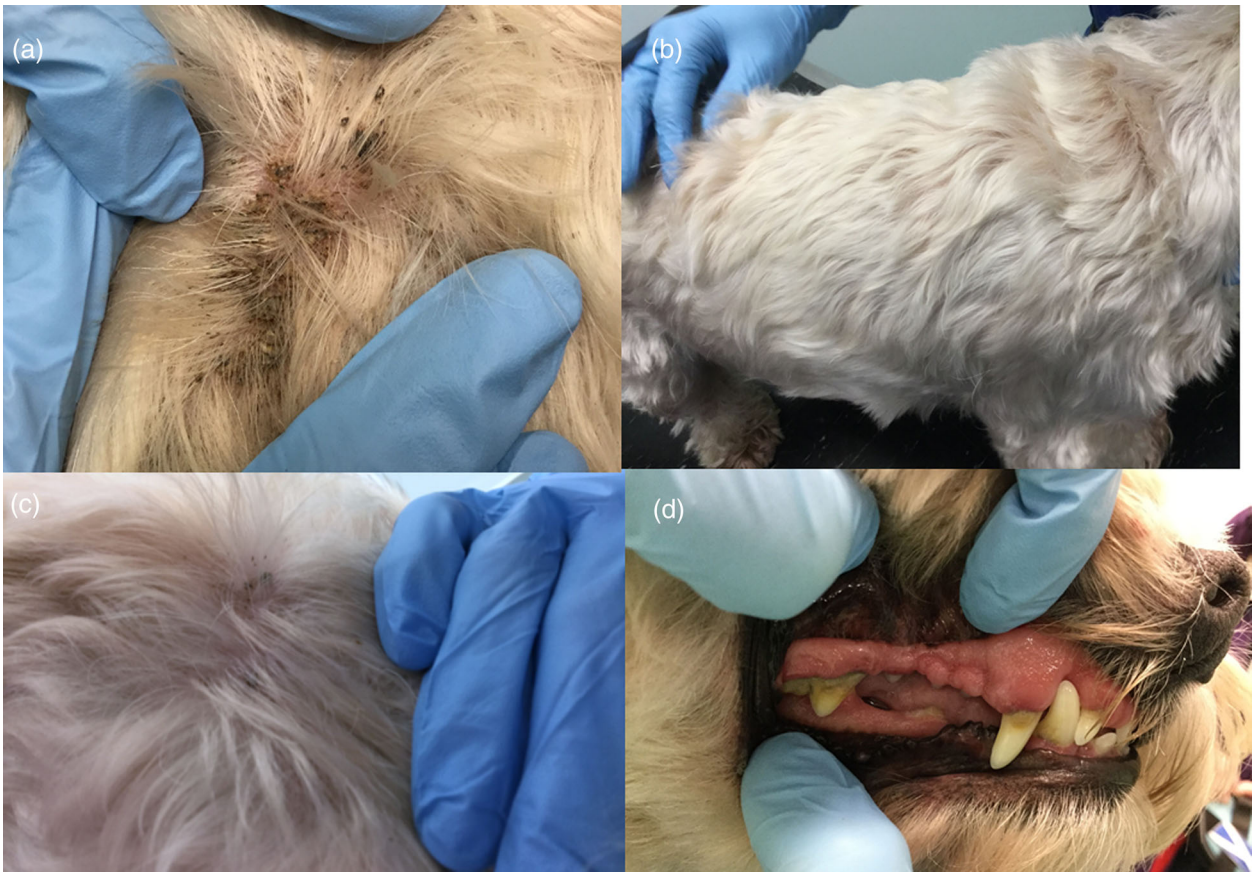

FIGURE 4 Resolving lesions after discontinuation of ciclosporin. Fourteen days after stopping ciclosporin, the crusty lesions due to psoriasiform-lichenoid dermatosis started disintegrating (a), while 28 days later, the lesions were almost fully resolved (b-c) and gingival hyperplasia remained stable (d)

psoriasiform-lichenoid dermatosis may be antibiotic-responsive since the lesions are reported to resolve quickly with the addition of systemic antibiotics. This has led to the postulation of a possible link between the development of psoriasiform-lichenoid dermatosis and an atypical staphylococcal presence. Antibiotics were not prescribed in this case due to isolation of the MRSP; thus, this case was not antibiotic-responsive, and the abnormalities were deemed to be related to the ciclosporin therapy, with partial resolution after 2 weeks, and then full clinical resolution achieved after 4 weeks.

The liver is the main site of metabolism for ciclosporin via the cytochrome P450 pathway. In this case, the dog was not on any medication that is known to have an impact on liver metabolism in dogs or humans. There was a concern that due to the previous history of PSS, the liver was not metabolising ciclosporin adequately. At the time of PSS ligation, the surgical report documented the presence of a small liver, which is common in dogs with PSS. Partial hepatectomy decreases drug clearance,[2] presumably due to reduced liver mass; thus, it is conceivable that a small liver size may not be able to fully metabolise all medications effectively.

Although all blood values and clinical signs associated with the PSS returned to normal after ligation, follow-up diagnostic imaging was not performed to assess the liver size. Measuring serum ciclosporin concentrations was considered a possibility. While this measurement shows a poor

correlation with clinical outcome and response to therapy, it may have been a valuable piece of information in this case since high levels may reflect poor metabolism. However, with both routine biochemistries including bile acids and fasted ammonia levels being normal, it was considered unlikely for the dog to have any liver dysfunction

The adverse effects noted in this case are therefore thought to be related to variable metabolism of ciclosporin[11] rather than altered metabolism due to liver disease.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

There were no ethical concerns in this case report, and therefore an ethical committee approval was not needed. The owner consented to the use of the data for research.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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