

Cutaneous nocardiosis in two dogs receiving ciclosporin therapy for the management of canine atopic dermatitis

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Background – Ciclosporin is a calcineurin inhibitor that is currently registered for the treatment of canine atopic dermatitis. The most common adverse effects include mild, transient gastrointestinal disturbances. Single case reports of opportunistic infections due to *Nocardia* spp., *Neospora* spp. and papillomaviruses have also been reported.

Hypothesis/Objectives – Clinicians should be aware of the potential risk of systemic immunosuppression and subsequent infection with *Nocardia* spp. in dogs receiving ciclosporin.

Animals – Cutaneous nocardiosis in two dogs receiving ciclosporin therapy for management of canine atopic dermatitis.

Methods – Histopathology, PCR for *Nocardia* spp. and computed tomography.

Results – One dog developed disseminated nocardiosis due to *Nocardia brasiliensis* and a second dog developed localized cutaneous nocardiosis due to a novel *Nocardia* species subsequent to ciclosporin administration at the recommended dose rate for the management of canine atopic dermatitis. The second case was receiving a combination of ciclosporin and ketoconazole, and serum trough ciclosporin levels were elevated.

Conclusions and clinical importance – Clinicians should be aware of the potential risk of systemic immunosuppression and subsequent infection with *Nocardia* spp. in dogs receiving ciclosporin. Measurement of serum ciclosporin levels may be useful in identifying those individuals which are at risk of opportunistic infections.

Introduction

Ciclosporin is a calcineurin inhibitor that is currently registered for the treatment of canine atopic dermatitis. Ciclosporin administration has been associated with *Nocardia* spp., *Neospora* spp. and papillomavirus infection in dogs but limited to single case reports.^{1–3} Localized and disseminated nocardiosis in two dogs is reported subsequent to ciclosporin being administered at registered dose rates for the management of canine atopic dermatitis.

Case 1

A 3-year-old female neutered West Highland white terrier with atopic dermatitis presented with multiple dermal nodules, lethargy and diarrhoea. Allergen-specific immunotherapy and ciclosporin (Neoral; Novartis Pharmaceuticals, North Ryde, Australia) 5 mg/kg orally once daily had

been administered for 4 months for management of atopic dermatitis.

Clinical findings

On physical examination, five firm, painful, subcutaneous nodules ranging in size from 10 to 23 mm in diameter with fistulous tracts draining serosanguinous fluid were located on the trunk and tail region. Marked diffuse gingival hyperplasia was evident.

A complete blood count and biochemical evaluation revealed mild hyperglycaemia. Multiple fine-needle aspirates of the nodules revealed pyogranulomatous inflammation, with Gram-positive, acid-fast, intracellular filamentous organisms in branch-like clusters with negative staining (Figures 1–3) confirmed by Ziehl–Neelsen staining. Enrofloxacin (Baytril; Bayer Healthcare, Pymble, Australia) 10 mg/kg orally once daily and doxycycline (Apex Laboratories, Somersby, Australia) 6.7 mg/kg orally twice daily were commenced with the presumptive diagnosis that these organisms were *Mycobacteria* spp. The ciclosporin was withdrawn.

Thoracic radiographs revealed a bronchial pattern, mild bronchiectasis, moderate tracheobronchial and cranial mediastinal lymph node enlargement and mild hepatomegaly. Histopathological evaluation of tissue biopsies revealed a moderate, chronic, multifocal pyogranulomatous dermatitis and panniculitis. Gram, periodic acid Schiff and Ziehl–Neelsen stains were negative. Microscopy and tissue culture and PCR testing of 16S rRNA

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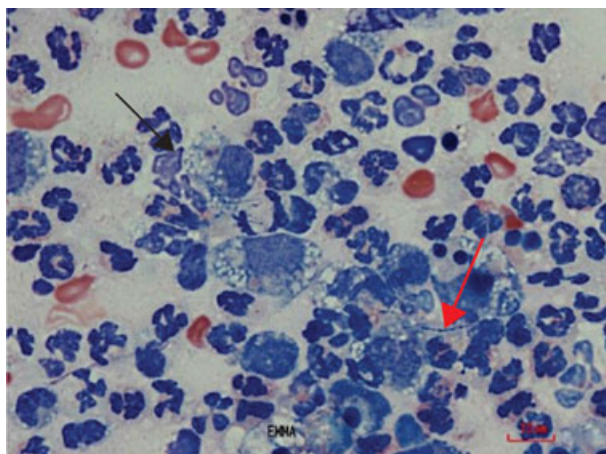


Figure 1. Case 1: Wright Giemsa staining of fine-needle aspirates of nodules, showing macrophages containing filamentous organisms (black arrow) with characteristic beaded appearance (red arrow).

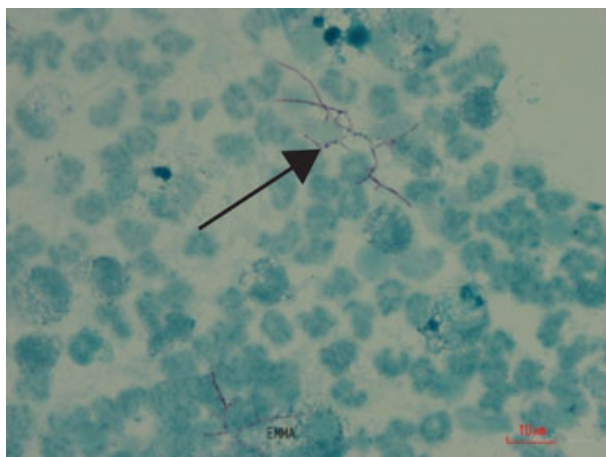


Figure 2. Case 1: Ziehl-Neelsen stain of fine-needle aspirates of nodules, showing acid-fast organisms (black arrow).

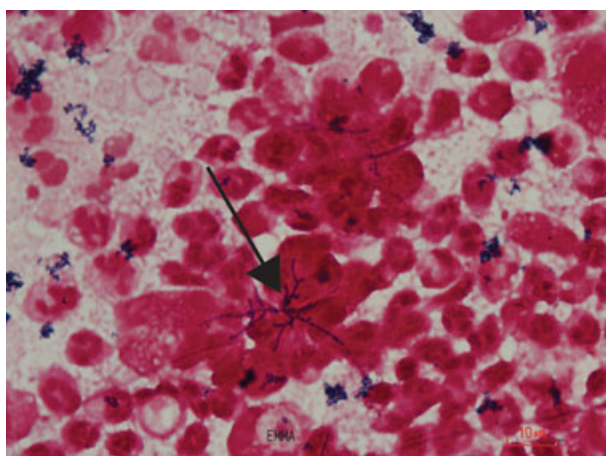


Figure 3. Case 1: Gram stain of fine-needle aspirates of nodules, showing Gram-positive organisms (black arrow).

identified *Nocardia brasiliensis* sensitive to amikacin, trimethoprim-sulfamethoxazole and moxifloxacin and resistant to ceftriaxone and meropenem based on the minimal inhibitory concentrations attained by E-testing.

Antimicrobial therapy was modified to moxifloxacin (Avelox; Bayer Healthcare, Pymble, Australia) 13.5 mg/kg orally once daily but withdrawn subsequent to seizure activity. Combination antimicrobial therapy with oral enrofloxacin and doxycycline was recommenced. All cutaneous nodules resolved within 4 weeks. The dog subsequently developed type I diabetes mellitus, and insulin (Caninsulin; MSD Animal Health, Bendigo East, Australia) replacement therapy was commenced.

Approximately 8 weeks after the original presentation, the dog presented with an acute, nonweightbearing lameness associated with a monostotic aggressive metaphyseal lesion affecting the left proximal humerus identified by computed tomography (Figure 4). Computed tomography-guided bone aspirates for microscopy, bacterial (aerobic and anaerobic) culture, susceptibility testing and PCR testing identified *Nocardia brasiliensis* with an identical antimicrobial susceptibility to the organism previously isolated.

Due to disease progression and risk of pathological fracture, the left forelimb was amputated. Bone culture confirmed the presence of an identical *Nocardia* isolate. Trimethoprim-sulfadiazine (Tribrissen; Jurox Pty Ltd, Rutherford, Australia) 24 mg/kg orally twice daily was prescribed. At the time of writing, the dog has been in remission for 14 months and remains diabetic.

Case 2

A 5-year, 7-month-old male entire atopic West Highland white terrier, receiving allergen-specific immunotherapy and ciclosporin (Neoral; Novartis Pharmaceuticals) 5 mg/kg orally once daily in conjunction with prednisolone (Pred-X 5; Apex Laboratories, Somersby, Australia) 0.3–



Figure 4. Case 1: Computed tomography image showing mixed osteolytic and proliferative lesion affecting the left proximal humerus.

0.6 mg/kg orally once daily to control pruritus for 3 years, presented with a rapidly enlarging mass in the left axillary region. Approximately 12 months prior to presentation, the dog developed calcinosis circumscripta and calcinosis cutis, and ketoconazole (Nizoral; Janssen-Cilag Pty Ltd, North Ryde, Australia) 5 mg/kg orally twice daily was introduced and prednisolone withdrawn.

Clinical findings

A firm, subcutaneous axillary mass, approximately 110 mm × 75 mm, with multiple fistulous draining tracts draining purulent to serosanguinous exudate was evident. There was moderate to marked gingival hyperplasia.

Haematological and biochemical evaluation was unremarkable. Trough serum ciclosporin concentrations were markedly elevated at 1780 µg/L. Histopathological evaluation of biopsy tissue revealed multinodular pyogranulomatous to suppurative panniculitis and dermatitis and long, filamentous, branching, Gram-positive, beaded, modified acid-fast bacteria confirmed as a *Nocardia* species sensitive to amikacin, cotrimoxazole, minocycline, moxifloxacin and meropenem and resistant to ceftriaxone based on minimal inhibitory concentrations attained by E-testing. Molecular testing using PCR of 16S rRNA for *Nocardia* spp. demonstrated no homology with any previously described *Nocardia* species. The ciclosporin and ketoconazole were withdrawn, and moxifloxacin 13.3 mg/kg orally once daily in combination with trimethoprim sulphonamide 30 mg/kg orally twice daily was initiated. Approximately 4 weeks later, there was some reduction in the size of the axillary mass but the dog developed a para-aural abscess and the owner elected euthanasia. Postmortem examination confirmed no other abnormalities. Bacterial culture of exudate from the abscess revealed a heavy mixed growth of nonhaemolytic *Escherichia coli* and *Staphylococcus pseudintermedius*. No *Nocardia* organisms were identified.

Discussion

Nocardia spp. are aerobic, Gram-positive, weakly acid-fast, ubiquitous soil saprophytic bacteria that cause opportunistic infections via inhalation or inoculation through skin. Canine nocardiosis typically occurs as one of three distinct clinical syndromes, namely a localized cutaneous/subcutaneous form, a pulmonary form and a systemic/disseminated form that typically involves lesions at two or more noncontiguous sites, with pulmonary involvement.⁴

Immunosuppression appears to be a predisposing factor for the development of nocardiosis in humans and cats, although both healthy and immunocompromised individuals can be affected.⁵ In dogs, infection occurs predominantly in immunocompromised individuals secondary to the administration of immunomodulatory drugs, including ciclosporin combined with or without ketoconazole, prednisolone, dexamethasone, cyclophosphamide, azathioprine, chlorambucil and aurothioglucose.^{1,6–8}

Ciclosporin inhibits neutrophil chemotaxis, degranulation and superoxide generation and has a specific cell-mediated immunomodulatory function via the inhibi-

tion of interleukin-2, which plays an important role in the activation and proliferation of T cells.^{9,10} The optimal ciclosporin serum concentrations required to control the clinical signs of canine atopic dermatitis are not clearly defined,^{11–13} but it is probable that elevated serum levels of ciclosporin result in marked immunosuppressive effects and thus predispose to the development of nocardiosis. We propose that it may be prudent to monitor the serum concentration of ciclosporin in dogs, as is currently recommended in cats, when screening for increased risk of opportunistic infection.¹⁴

Ciclosporin administration has been previously implicated as a predisposing factor for the development of disseminated canine nocardiosis.^{1,7,8} The evidence would suggest that nocardiosis can develop as a rare complication of ciclosporin administered at both registered dose rates over a short time period and at extralabel dosage rates, either with or without the combination of other immunomodulatory or potentiating agents. Although the incidence of this complication is very low, we conclude that neither the length of ciclosporin therapy nor whether ciclosporin is combined with other potentiating drugs, such as ketoconazole, influences the risk of developing infection.

Diabetes mellitus has been reported in a dog suspected to be prediabetic receiving prednisolone and ciclosporin for management of immune-mediated anaemia.¹⁵ Ciclosporin suppresses insulin secretion and can cause β-cell destruction, and may accelerate the development of diabetes in predisposed dogs.¹⁵ In case 1, ciclosporin was administered for 4 months, and the patient developed permanent diabetes mellitus despite ciclosporin drug withdrawal. Blood and urine monitoring for hyperglycaemia and glucosuria is recommended for dogs receiving ciclosporin that may be predisposed to the development of diabetes mellitus.

In both our cases, the identification of bacterial organisms was confirmed using 16S ribosomal DNA sequencing, which is a useful method for both the confirmation and the speciation of *Nocardia* spp. organisms.^{16–21} The speciation of the organism is especially important in these cases because species have varying antimicrobial susceptibilities, and the selection of antimicrobial therapy for the treatment of disseminated nocardiosis can be challenging. We elected to use the antimicrobial moxifloxacin, a fourth generation fluoroquinolone, which is highly effective for the treatment of human pulmonary nocardiosis.^{22,23} The most common adverse effects reported in humans include nausea, vomiting and diarrhoea, but seizures are documented.²³ The exact pathogenesis of the neurotoxic effects is unknown but may be due to drug interaction with the γ-aminobutyric acid (an inhibitory neurotransmitter) receptor, as well direct activation of *N*-methyl-D-aspartate (NMDA) and adenosine receptor mechanisms.^{23,24} Moxifloxacin was well tolerated in one dog (case 2), but the therapy had to be withdrawn in one case (case 1) due to seizure activity. Further investigation is required to evaluate the efficacy of moxifloxacin as a first-line treatment option against canine disseminated nocardiosis and the frequency of adverse effects.

Conclusion

Ciclosporin is a drug frequently used for the management of canine atopic dermatitis. Clinicians should be aware of the potential risk of systemic immunosuppression and subsequent infection with *Nocardia* spp. Early recognition of clinical signs, especially the acute onset of single or multiple cutaneous nodules, combined with appropriate diagnostic intervention, with fine-needle aspirate, tissue culture and speciation with culture and susceptibility testing, will improve the prognosis. Moxifloxacin may be an effective first-line empirical antibiotic choice for canine disseminated nocardiosis. Further studies are required to identify the factors that increase the risk of opportunistic infection in susceptible individuals. It may be advisable to consider the routine measurement of serum ciclosporin levels in dogs.

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Résumé

Contexte – La cyclosporine est un inhibiteur de la calcineurine, actuellement enregistré dans le traitement de la dermatite atopique canine. Les effets secondaires les plus fréquents sont des troubles gastro-intestinaux modérés et transitoires. Des cas isolés d'infections opportunistes dues à *Nocardia* spp., *Neospora* spp. et papillomavirus ont aussi été rapportés.

Hypothèses/Objectifs – Les cliniciens devraient être avertis du risque potentiel d'immunosuppression systémique et d'infection subséquente à *Nocardia* spp. chez les chiens recevant de la cyclosporine.

Sujets – Deux chiens présentant une nocardiose cutanée et recevant de la cyclosporine pour le traitement de leur dermatite atopique.

Méthodes – Histopathologie, PCR pour *Nocardia* spp. et tomographie à densité.

Résultats – Un chien a développé une nocardiose disséminée due à *Nocardia brasiliensis* et un autre chien a développé une nocardiose cutanée localisée due à une nouvelle espèce de *Nocardia* suite à l'administration de cyclosporine à la dose indiquée dans la gestion de la dermatite atopique canine. Le deuxième cas a

reçu une association de cyclosporine et de kétoconazole et les taux sériques de cyclosporine étaient élevés.

Conclusions et importance clinique – Les cliniciens doivent être avertis du risque potentiel d'immunosuppression systémique et d'infection consécutive à *Nocardia* spp chez les chiens recevant de la cyclosporine. Les mesures de cyclosporine sérique pourraient être utiles dans l'identification des individus à risque d'infections opportunistes.

Resumen

Introducción – la ciclosporina es un inhibidor de la calcineurina que esta actualmente registrado para el tratamiento de la dermatitis atópica canina. Los efectos adversos mas frecuentes incluyen trastornos gastrointestinales ligeros y transitorios. Se han publicado casos aislados de infecciones oportunistas con *Nocardia* spp., *Neospora* spp. y papilomavirus.

Hipótesis/Objetivos – los clínicos deben ser conscientes del riesgo potencial de inmunosupresión sistémica e infecciones oportunistas causadas por *Nocardia* spp. en perros tratados con ciclosporina.

Animales – nocardiosis cutánea en dos perros tratados con ciclosporina para el manejo de la dermatitis atópica canina.

Métodos – citopatología, PCR para *Nocardia* spp. y tomografía computerizada.

Resultados – un perro desarrolló nocardiosis diseminada debido a *Nocardia brasiliensis* y un segundo perro desarrolló nocardiosis cutánea localizada debido a una nueva especie de *Nocardia* tras la administración de ciclosporina a las dosis recomendadas para el manejo de la dermatitis atópica canina. El segundo caso estaba recibiendo una combinación de ciclosporina y ketoconazol y los niveles de ciclosporina en el suero estaban elevados.

Conclusiones e importancia clínica – los clínicos deben tener en cuenta el riesgo de inmunosupresión sistémica llevando a infecciones con *Nocardia* spp. en perros tratados con ciclosporina. La evaluación de los niveles de ciclosporina en suero puede ser útil para identificar aquellos animales con riesgo de contraer infecciones oportunistas.

Zusammenfassung

Hintergrund – Ciclosporin ist ein Calcineurin Inhibitor, der zurzeit für die Behandlung der atopischen Dermatitis des Hundes zugelassen ist. Die häufigsten Nebenwirkungen beinhalten milde, transiente gastrointestinale Störungen. Einzelne Fallberichte opportunistischer Infektionen durch *Nocardia* spp., *Neospora* spp. und Papillomaviren gibt es ebenfalls.

Hypothese/Ziele – Kliniker sollten sich des möglichen Risikos einer systemischen Immunsuppression und nachfolgender Infektion mit *Nocardia* spp. bei Hunden, die Ciclosporin erhalten, bewusst sein.

Tiere – Es wurden zwei Hunde mit kutaner Nocardiose verwendet, die zum Management ihrer atopischen Dermatitis Ciclosporin als Therapie erhielten.

Methoden – Histopathologie, PCR für *Nocardia* spp. und Computertomographie.

Ergebnisse – Ein Hund entwickelte eine disseminierte Nocardiose aufgrund von *Nocardia brasiliensis* und ein zweiter Hund entwickelte eine lokalisierte Nocardiose aufgrund einer neuen *Nocardia* Spezies. Letzteres erfolgte während einer Ciclosporinverabreichung in der empfohlenen Dosis zum Management der caninen atopischen Dermatitis. Der andere Fall erhielt eine Kombination aus Ciclosporin und Ketokonazol, wobei die Serumschwellwerte von Ciclosporin erhöht waren.

Schlussfolgerungen und klinische Bedeutung – Die Kliniker sollten sich des potentiellen Risikos einer systemischen Immunsuppression und nachfolgender Infektion mit *Nocardia* spp. bei Hunden, die Ciclosporin erhalten, bewusst sein. Die Messungen von Ciclosporinwerten könnten beim Identifizieren dieser Individuen, die zu den Risikopatienten bezüglich opportunistischer Infektionen gehören, nützlich sein.

要約

背景 - シクロスポリンはカルシニューリン阻害薬であり、イヌアトピー性皮膚炎として治療に近年認可された。最も一般的な有害事象には軽度で一時的な胃腸障害が含まれる。*Nocardia* spp.、*Neospora* spp. ならびにパピローマウイルスを原因とする日和見感染症の症例が報告されている。

仮説/目的 - 臨床家はシクロスポリンを投与しているイヌの全身性免疫抑制の可能性および *Nocardia* spp. による二次感染に注意すべきである。

供与動物 - イヌアトピー性皮膚炎の管理のためにシクロスポリンでの治療を受けていた皮膚ノカルジア症のイヌ 2 頭

方法 - 病理組織、*Nocardia* spp. に対する病理組織、PCR およびコンピューター断層撮影

結果 - イヌアトピー性皮膚炎の維持に奨励されている薬用量でシクロスポリンを投与していた、1 頭のイヌは *Nocardia brasiliensis* に起因した散在性のノカルジア症を、2 頭目のイヌは新規の *Nocardia* 種に起因した限局性皮膚ノカルジア症を二次的に生じていた。2 症例目はシクロスポリンとケトコナゾールを併用して投与され、血清トラフシクロスポリン値は上昇していた。

結論と臨床的な重要性 - 臨床家はシクロスポリンを投与されているイヌにおいて、全身性免疫抑制および *Nocardia* spp. による二次感染症の潜在的リスクに注意するべきである。血清シクロスポリン値は日和見感染のリスクがあるイヌを特定するのに有益かもしれない。

摘要

背景 - 环孢素是一种神经钙调蛋白抑制剂，目前注册用于治疗犬异位性皮炎。最常见的不良反应包括轻度、短暂的胃肠道紊乱。诺卡氏菌、新孢子虫和乳头状瘤病毒引起的条件性感染的单个病例报告也曾被发表。

假设/目的 - 临床医生应知道犬接受环孢素治疗后，全身性免疫抑制有继发诺卡氏菌感染的潜在风险。

动物 - 2只皮肤诺卡氏菌病的异位性皮炎患犬，接受过环孢素治疗。

方法 - 组织病理学、诺卡氏菌PCR和计算机断层扫描。

结果 - 使用推荐剂量频率的环孢素管理犬异位性皮炎后，巴西诺卡氏菌引起1只犬的弥散性诺卡氏菌病，新型诺卡氏菌引起第二只犬的局部皮肤诺卡氏菌病。第二个病例接受了环孢素和酮康唑结合治疗，使环孢素的血清低值水平提高了。

结论和临床价值 - 临床医生应了解，接受环孢素治疗后的犬，有全身性免疫抑制和诺卡氏菌感染的潜在风险。血清环孢素水平的测量，可能对识别那些有条件性感染风险的个体有用。