Cyclosporine induced generalized hyperkeratosis in a dog

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Cyclosporin induzierte generalisierte Hyperkeratose bei einem Hund

Cyclosporin ist ein starkes immunsuppressives Mittel, das in der Veterinärmedizin zur Behandlung einer Vielzahl von entzündlichen oder immunvermittelten Erkrankungen verwendet wird. Viele Nebenwirkungen sind mit diesem Medikament verbunden, die meisten davon treten jedoch selten auf. Eine 5 Jahre alte, weibliche intakte französische Bulldogge wurde mit multiplen, multifokal verteilten, schweren hyperkeratotischen und papillomatösen/verrukösen Plaques vorgestellt. Der Hund wurde wegen einer Meningoenzephalitis unbekannter Ursache (MUO) mit Cyclosporin über einen langen Zeitraum behandelt. Vorgeschichtlich wurde eine atopische Dermatitis und Calcinosis cutis diagnostiziert. Eine Papillomavirus-Infektion wurde durch Polymerase-Kettenreaktion (PCR) ausgeschlossen, und die histopathologische Analyse ergab eine chronische lymphoplasmatische unspezifische Dermatitis, Perifollikulitis und Periadnexitis sowie eine fokale Follikulitis mit papillomatöser epidermaler Hyperplasie und orthokeratotischer Hyperkeratose. Es wurde die Diagnose „Cyclosporin-induzierte epidermale Hyperplasie mit sekundärer Pyodermie“ gestellt. Das Cyclosporin wurde abgesetzt und um die MUO zu kontrollieren stattdessen eine Therapie mit Mycophenolatmofetil begonnen. Eine antimikrobielle Behandlung wurde für drei Wochen verschrieben. Nach vier Monaten waren die Hautläsionen vollständig abgeheilt. Bis heute zwei Jahre nach Therapiewechsel ist der Hund immer noch in Remission.

Das Auftreten von hyperplastischen Läsionen im Zusammenhang mit einer Cyclosporin-Therapie wurde in früheren Publikationen beschrieben. Die meisten von ihnen ähneln denen der psoriasiformen lichenoiden Dermatitis, obwohl in einigen Fällen das Papillomavirus nachgewiesen werden kann. Der Hund des vorliegenden Falles zeigte vergleichbare Auffälligkeiten im histopathologischen Befund, jedoch konnte eine Papillomavirus-Beteiligung mittels PCR ausgeschlossen werden. Wie in einem früheren Bericht beobachtet, gab es keine Korrelation zwischen dem Cyclosporin-Blutspiegel und dem Schweregrad dermatologischer Veränderungen. Ein Absetzen von Cyclosporin führte zu einer vollständigen Heilung in 4 Monaten. Dieser Fall unterstreicht die Bedeutung einer regelmässigen Überwachung und Nachkontrolle bei Patienten

Abstract

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Cyclosporine is a potent immunosuppressive agent used in veterinary medicine to treat a variety of inflammatory or immune mediated conditions. Many adverse effects are associated with this medication, however most of them rarely occur. A 5-year-old, female intact French bulldog was presented with multiple, multifocally distributed, severe hyperkeratotic and papillomatous/verrucous plaques. The dog was on long-term immunosuppressive treatment with cyclosporine for meningoencephalitis of unknown origin (MUO). It had an history of atopic dermatitis and calcinosis cutis. A papillomavirus infection was excluded by polymerase chain reaction (PCR), and histopathologic analysis revealed a chronic lymphoplasmacytic non-specific dermatitis, perifolliculitis and periadnexitis and focal folliculitis with papillomatous epidermal hyperplasia and orthokeratotic hyperkeratosis. The diagnosis of “cyclosporine-induced epidermal hyperplasia with secondary pyoderma” was made. Cyclosporine was discontinued and as an alternative mycophenolate mofetil was started to control the MUO. An antimicrobial treatment was prescribed for three weeks. After four months, the skin lesions had healed completely. To date after 2 years, the dog is still in remission.

The occurrence of hyperplastic lesions associated with cyclosporine therapy have already been described in previous reports. Most of them resemble those of psoriasiform lichenoid dermatitis, although papilloma virus may be detected in some instances. The dog of the present case showed some peculiarities in the histopathological findings, and a papillomavirus involvement was ruled out with PCR. Like observed in a previous report, there was no correlation between cyclosporine blood level and the severity of dermatological changes. A discontinuation of cyclosporine resulted in complete healing in 4 months. This case highlights the importance of regular monitoring and follow-ups in patients on immunosuppressive therapy. Even rare side effects should always be considered in these cases.

Keywords: cyclosporine, dog, hyperkeratosis, immunosuppression, side effects

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unter immunsuppressiver Therapie. Auch seltene Nebenwirkungen sollten in diesen Fällen immer bedacht werden.

Schlüsselwörter: Cyclosporin, Hund, Hyperkeratose, Immunsuppression, Nebenwirkungen

Introduction

Cyclosporine is a potent immune suppressive agent that has been used for several decades in human medicine to prevent transplant rejections and treat dermatological conditions, such as psoriasis and atopic dermatitis.[11] It selectively inhibits calcineurin, thereby impairing the transcription of IL-2 and several other cytokines necessary for the activation of T-helper lymphocytes.[20] In veterinary medicine this medication has been approved for the treatment of atopic dermatitis and a variety of other inflammatory- or immune mediated conditions including meningoencephalitis of unknown origin (MUO).[1] There have been many adverse effects associated with cyclosporine-treatment in dogs, however, most of them rarely occur, outside of general gastrointestinal problems which are not uncommon.[2] Hyperplastic skin lesions are one of those rare adverse effects. In human medicine, most lesions appear to be induced by papilloma virus infections.[14] Hyperplastic lesions in dogs occasionally develop, and most of them resemble those of psoriasiform lichenoid dermatitis, although papilloma virus may be detected in some instances.[7]and polymerase chain reaction (PCR In the present case report, we describe the clinical and histopathological features of a case of hyperplastic skin lesions in a dog under long-term cyclosporine treatment.

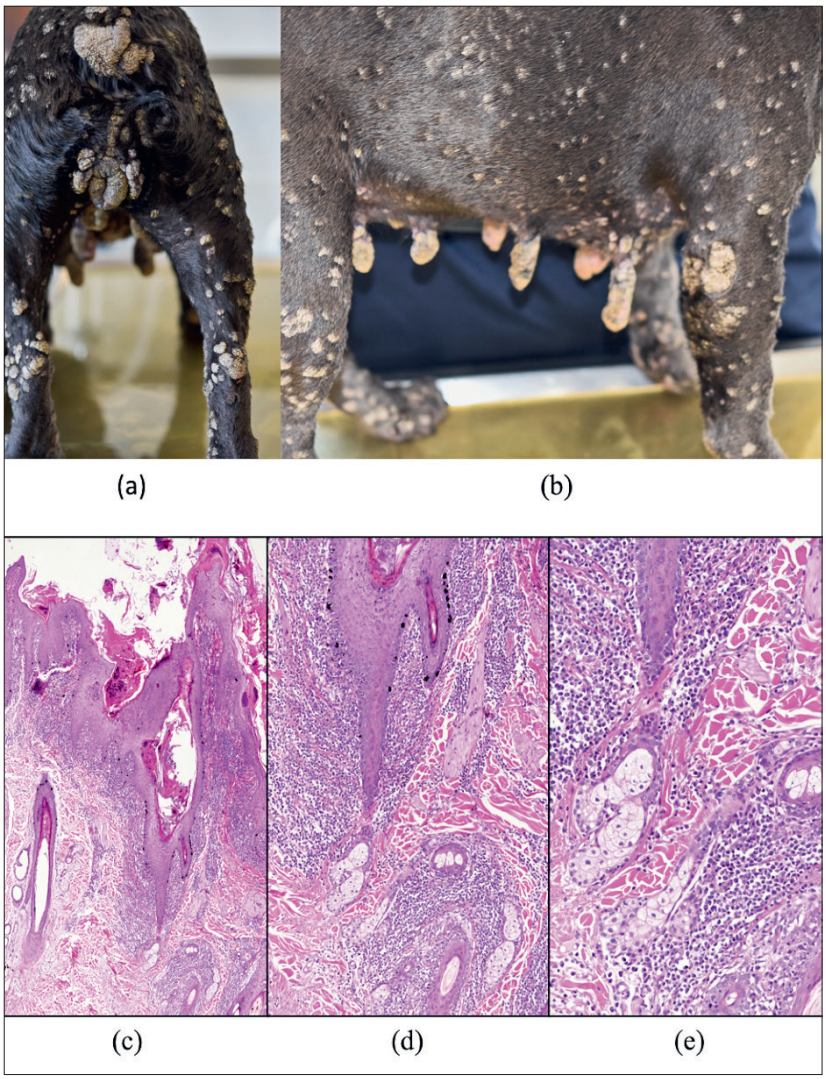

Figure 1: Clinical (a–b) and histopathological (c–e) features of a 5-year-old intact French bulldog skin lesions. (a) Hyperkeratotic and papillomatous/verrucous plaques, distributed over the hind extremities. The vulva showed also hyperkeratotic changes. (b) Similar skin lesions were present on the lateral aspect of the legs, hips and thorax. The nipples were severely enlarged and hyperkeratotic.

(c-e) Histological image from a lesion on the back. The skin showed papillomatous epidermal protrusions with moderate epidermal orthokeratotic hyperkeratosis, epidermal hyperplasia with moderate dermal, perifollicular and periadnexal lympho-plasmacytic infiltration. HE stain, c) ×4, d) ×10, e) ×20.

Case report

A 5-year-old intact French bulldog with an history of meningoencephalitis of unknown origin (MUO) and atopic dermatitis was presented to our dermatology department because of severe hyperplastic skin lesions.

The MUO diagnosis was made four years previous to this event. When the diagnosis occurred, immunosuppressive treatment with prednisolone 1 mg/kg twice daily and cyclosporine 5 mg/kg twice daily was prescribed and started. The prednisolone dose was then gradually reduced, but the neurological signs relapsed several times. These neurological complications led to a long-term therapy with low dose prednisolone and cyclosporine.

Three years later the dog was presented again at the clinic due to the development of calcinosis cutis and secondary pyoderma. At this time, the dog was receiving cyclosporine 5 mg/kg twice daily and prednisolone 0,1 mg/kg every third day. The dog was treated with systemic antibiotic (cefalexin 25 mg/kg twice daily for four weeks) and antiseptic shampoo. Discontinuation of prednisolone was recommended, but the dog had shown several relapses whenever the prednisolone was reduced below 0,4 mg/kg/day, preventing its

immediate reduction/discontinuation. Serum cyclosporine level at this time point was 280 ng/ml. Options of alternative immunosuppressive treatment including increase of the cyclosporine to 400 ng/ml [1] were discussed. Therefore cyclosporine was increased to 15 mg/kg BID and prednisolone was slowly reduced over the following nine months and then discontinued. Calcinosis cutis went into remission three weeks after discontinuation of prednisolone.

Five months later, the dog had developed multiple, progressive skin lesions over the last three months. He was still receiving cyclosporine 15 mg/kg twice daily and no prednisolone since the last visit five months ago. Multiple, multifocally distributed, severe hyperkeratotic and papillomatous/verrucous plaques were present (Figure 1 a, b). The dog had generalized moderate pododermatitis and bilateral moderate otitis externa with yeasts, rods and cocci. The main differential diagnoses for the papillomatous skin lesions were either a papillomavirus infection or a cyclosporine-induced psoriasiform lichenoid dermatitis.

A blood test was performed which revealed a slight decrease in total protein, albumin, sodium, potassium, phosphate and cholesterol, moderate thrombocytosis, mild monocytosis and lymphopenia. The blood level of cyclosporine was 133 ng/ml. Punch biopsies of papillomatous like lesions, present on the trunk, limb and head were taken, and a skin sample was sent to the laboratory for papillomavirus PCR. The PCR was negative, and histopathological samples from lesions on the back revealed a mild to moderate chronic lympho-plasmacytic non-specific dermatitis, perifolliculitis and periadnexitis and focal folliculitis with papillomatous epidermal hyperplasia and orthokeratotic hyperkeratosis. The diagnosis of «cyclosporine-induced epidermal hyperplasia with secondary pyoderma» was made. A psoriasiform lichenoid dermatitis was widely ruled out morphologically in the absence of a parakeratosis,.

Cyclosporine was tapered and discontinued within four weeks, and alternative immunomodulatory treatment options have been discussed with the owner. The owner elected treatment with mycophenolate mofetil which was dosed orally10 mg/kg twice daily. An antimicrobial treatment (cefalexin 25 mg/kg twice daily) and antiseptic shampoo every-other-day were prescribed for three weeks. After 4 months, the dog was presented for a follow-up: the skin lesions had healed completely (Figure 2). No neurological signs were present. Treatment with mycophenolate mofetil was continued. To date after 2 years, the dog has not shown any relapses.

Discussion

Immune mediated diseases requiring the long-term use of potent immunosuppressive – and immunomodulating drugs need to be controlled. Glucocorticoids are the most commonly used class of drugs for these indications.[16] In the past, they were administered in high doses, with the associated side effects. However in the preceding decades, new therapeutic approaches have been evaluated, and today more options are available to control these diseases.[17] Cyclosporine is a potent drug, used to treat various inflammatory- and autoimmune diseases in veterinary medicine. Cyclosporine (with target levels of 200–400 ng/ml in peripheral blood) has been recommended as one possible treatment option for MUO in dogs.[1] Although many adverse effects are associated with this treatment in dogs, most of them are uncommon.[2]

In the case presented here, an immunosuppressive treatment with prednisolone and cyclosporine was initiated to control the dog's neurological condition. Over the course of years, adverse effects of both drugs appeared: first a calcinosis cutis, followed by hyperplastic skin lesions after increasing the dosage of cyclosporine.

Calcinosis cutis describes a rare condition where inorganic calcium crystals are deposited in the dermis, subcutis or rarely epidermis.[25] The mechanism by which calcification occurs is usually divided in four categories: dystrophic, iatrogenic, metastatic and idiopathic.[24] Dystrophic is the most common type, and it is associated with tissue damage. Metastatic refers to an abnormal calcium metabolism with consequent accumulation in healthy tissue; iatrogenic appears secondary to penetration of products containing calcium and in idiopathic calcification no cause is found.[24] A recent study involving 46 dogs documents iatrogenic hyperadrenocorticism as the major cause of calcinosis cutis in the included dogs, followed by endogenous hyperadrenocorticism and underlying renal disease.[6] The cutaneous lesions consist in erythematous papules, plaques and nodules,

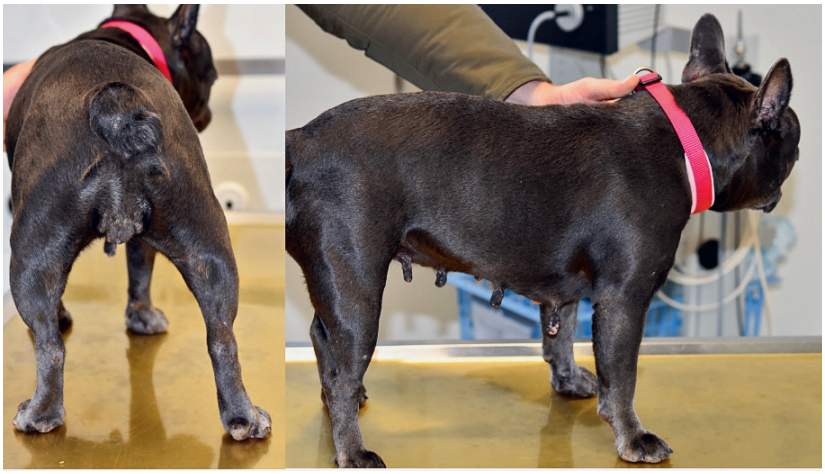

Figure 2: Clinical pictures of a 5-year-old intact French bulldog with an history of cyclosporine induced generalized hyperkeratosis at the follow-up 4 months after cyclosporine withdrawal and mycophenolate mofetil initiation. A complete remission of the papillomatous skin lesions was achieved.

which may get ulcerated and secondarily infected. The underlying cause should be identified and, whenever possible, removed. In addition, in human medicine several treatment options are reported, such as minocycline, warfarin, probenecid, colchicine, diltiazem.[19] No standard therapy has been accepted for dogs so far. Successful treatments with dimethylsulfoxide gel (DMSO) or mynocicline are reported.[3,5,15] In the present case, the dog suffered of dystrophic calcification caused by iatrogenic hyperadrenocorticism. He achieved complete healing of the calcinosis cutis lesion after discontinuation of the prednisolone treatment.

The development of hyperplastic skin lesions in dogs treated with cyclosporine has been described as a rare side effect in previous studies.[7,18,22,26]and polymerase chain reaction (PCR In the dog presented here a cyclosporine dosage of 30 mg/kg/day induced such lesions, mirroring data from literature reporting inducing dosages ranging from three to 30 mg/kg/day.[7,22,26]and polymerase chain reaction (PCR One study in particular also reported on cyclosporine blood levels: these ranged from less than 100 ng/ml to 2258 ng/ml.[22] Interestingly, these blood level did not correlate with the severity of clinical lesions. In the present case, the cyclosporine blood levels at presentation were 133 ng/ml, falling within the above reported range, but even in the lower recommended range for treatment of immunomodulated diseases.[1] The dog showed higher blood cyclosporine values when the dosage was lower at treatment begin. The blood samples were taken at different time points after medication intake, which may explain the inconsistencies.

The previously described treatment duration until onset of hyperplastic skin lesions also varies greatly, from a minimum of three weeks to a maximum of two years. In our case it is difficult to establish exactly when the first skin lesions appeared, since the owner waited some months before presenting the dog. Considering the medical history, we can deduce that the first lesions appeared approximately three years and eight months after starting the cyclosporine, and approximately eight months after increasing the dosage to 30 mg/kg daily. In early disease stage, the skin lesions are described as multiple small, variably pigmented, slightly raised verrucous papules or plaques, mostly affecting the head and limbs. With time, these progress to irregular, hyperkeratotic, papillomatous, firm diffusely distributed plaques. Histologically acanthosis, hyperkeratosis with focal parakeratosis, intraepidermal pustules and lichenoid dermal inflammation, predominately composed of lymphocytes and plasma cells are observed. Bacteria in follicular infundibula or stratum corneum are also reported in almost all cases. These lesions and histological findings resemble those reported as psoriasiform lichenoid dermatitis of springer spaniels.[13] Only one study reports histological findings that do not coincide with this disease, i.e. a moderate hyperplasia of hair follicles and sebaceous glands.[22] It is interesting to note that the histological pattern of the dog presented herein lacks a typical feature of a psoriasiform lichenoid dermatitis: the focal parakeratosis. It has been hypothesized that this hyperplastic skin reaction is induced by an excessive reaction to staphylococcal infection, and it reportedly respond to antibacterial treatment.[4] In a previous case series, however, the lesions regressed in three out of eight dogs without the administration of antimicrobials after discontinuation or decreasing the administration of cyclosporine.[7]and polymerase chain reaction (PCR In addition, similar lesions went in remission in all 12 dogs included in another study within eight weeks after complete discontinuation of cyclosporine treatment.[22] In all reported cases, including the dog of the present case report, antimicrobials were administered, in conjunction with a reduction or complete withdrawal of cyclosporine. Improvements were observed at the earliest after one week, and a complete resolution of symptoms between two and four months.

Cyclosporine causes an increased production of extracellular dermal matrix, associated with secretion of transforming growth-factor- β, which is known to cause gingival hyperplasia in humans.[23] This property may explain the development of the hyperplastic cutaneous lesions.

Another possible pathomechanism of the hyperplasia may be an opportunistic papillomavirus infection, as reported in humans.[14] Papilloma virus DNA was amplified by the samples in two out of nine dogs in a previous study.[7]and polymerase chain reaction (PCR In one of these dogs the lesions were removed surgically, whereas in the other dog, interestingly, they regressed after the dosage of cyclosporine was reduced.[7]and polymerase chain reaction (PCR

In the case presented here, we describe the occurrence of two adverse effects caused by immunosuppressive drugs in a dog: calcinosis cutis caused by prednisolone, and hyperplastic skin lesions caused by cyclosporine. Both of these adverse effects resolved completely following discontinuation of the responsible drug, and the use of a respective replacement. Concerning the hyperplastic lesions, one important differential diagnosis must always be taken into account, namely an infection with papillomavirus. In fact, in two cases, reported in the literature, papillomavirus infections have caused similar hyperplastic and verrucous skin lesions.[7]and polymerase chain reaction (PCR

This case report highlights the importance of careful monitoring and regular check-ups in patients on immunosuppressive therapy. This holds not only true for cyclosporine, but also for other immunosuppressive drugs that are used for MUO treatment, since all come with potential severe side effects. [8–10,12,21] No gold standard exits for the treatment of MUO and no matter what treatment is chosen it is important to be aware also of rare side effects. The control of adverse reactions can in some cases be complicated and time-consuming. The data of the existing literature do not

show a correlation between the dosage and blood levels of cyclosporine and the severity of the hyperplastic lesions. Monitoring of cyclosporine blood levels may therefore not be a valid parameter for dose adjustment in these cases, and clinical evaluation may be more appropriate.

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Hyperkératose généralisée induite par la cyclosporine chez un chien

La cyclosporine est un puissant agent immunosuppresseur utilisé en médecine vétérinaire pour traiter une variété de conditions inflammatoires ou à médiation immunitaire. De nombreux effets indésirables sont associés à ce médicament, mais la plupart d'entre eux se produisent rarement. Un bouledogue français intact, âgé de 5 ans, a été présenté avec de multiples plaques hyperkératosiques et papillomateuses/verruqueuses sévères, réparties de manière multifocale. Le chien suivait un traitement immunosuppresseur à long terme à base de cyclosporine pour une méningo-encéphalite d'origine inconnue (MUO). Il avait des antécédents de dermatite atopique et de calcinosis cutis. Une infection à papillomavirus a été exclue par réaction en chaîne par polymérase (PCR) et l'analyse histopathologique a révélé une dermatite chronique lymphoplasmocytaire non spécifique, une périfolliculite et une périannexite ainsi qu'une folliculite focale avec hyperplasie épidermique papillomateuse et hyperkératose orthokératosique. Le diagnostic d'»hyperplasie épidermique induite par la cyclosporine avec pyodermie secondaire» a été posé. La cyclosporine a été stoppée et on a commencé à administrer du mycophénolate mofétil comme alternative pour contrôler l'OMU. Un traitement antimicrobien a été prescrit pendant trois semaines. Après quatre mois, les lésions cutanées étaient complètement guéries. À ce jour, après deux ans, le chien est toujours en rémission.

L'apparition de lésions hyperplasiques associées au traitement par la cyclosporine a déjà été décrite dans des rapports précédents. La plupart d'entre elles ressemblent à celles de la dermatite lichénoïde psoriasiforme, bien que le virus du papillome puisse être détecté dans certains cas. Le chien du cas présent présentait quelques particularités dans les résultats histopathologiques et une implication du papillomavirus a été exclue par PCR. Comme observé dans un rapport précédent, il n'y avait pas de corrélation entre le taux sanguin de cyclosporine et la sévérité des altérations dermatologiques. L'arrêt de la cyclosporine a permis une guérison complète en 4 mois. Ce cas souligne l'importance d'une surveillance et d'un suivi réguliers des patients sous traitement immunosuppresseur. Les effets secondaires, même rares, doivent toujours être pris en compte dans ces cas.

Mots clés: cyclosporine, chien, hyperkératose, immunosuppression, effets secondaires

Ipercheratosi generalizzata indotta da ciclosporina in un cane

La ciclosporina è un potente agente immunosoppressivo utilizzato in medicina veterinaria per trattare una serie di condizioni infiammatorie o immunomediate. Molti effetti secondari sono associati a questo farmaco, ma la maggior parte di questo si verifica raramente. Una femmina intatta di bulldog francese di 5 anni è stata presentata con placche ipercheratotiche e papillomatose/verrucose multiple, distribuite in modo multifocale. Il cane era in trattamento immunosoppressivo a lungo termine con ciclosporina per una meningoencefalite di origine sconosciuta (MUO). Aveva un'anamnesi di dermatite atopica e calcinosi cutis. L'infezione da papillomavirus è stata esclusa mediante la reazione a catena della polimerasi (PCR) e l'analisi istopatologica ha rivelato una dermatite linfoplasmacitica cronica aspecifica, perifollicolite e periadesione e follicolite focale con iperplasia epidermica papillomatosa e ipercheratosi ortocheratotica. La diagnosi posta era di «iperplasia epidermica indotta da ciclosporina con piodermite secondaria». La ciclosporina è stata sospesa e come alternativa è stato iniziato un trattamento con micofenolato mofetile per controllare la MUO. È stato anche prescritto un trattamento antimicrobico per tre settimane. Dopo quattro mesi, le lesioni cutanee erano completamente guarite. Ad oggi, dopo 2 anni, il cane è ancora in remissione.

La comparsa di lesioni iperplastiche associate alla terapia con ciclosporina è stata descritta in pubblicazioni precedenti. La maggior parte di queste assomigliano a quelli della dermatite lichenoide psoriasiforme, anche se in alcuni casi è possibile rilevare la presenza di papillomavirus. Il cane del presente caso ha mostrato anomalie comparabili nei risultati istopatologici, ma il coinvolgimento del papillomavirus è stato escluso dalla PCR. Come osservato in un precedente rapporto, non vi era alcuna correlazione tra i livelli ematici di ciclosporina e la gravità delle alterazioni dermatologiche. L'interruzione della ciclosporina ha portato alla guarigione completa in 4 mesi. Questo caso evidenzia l'importanza di un monitoraggio e di un seguito regolari nei pazienti in terapia immunosoppressiva. Anche gli effetti collaterali rari devono sempre essere presi in considerazione in questi casi.

Parole chiave: ciclosporina, cane, ipercheratosi, immunosoppressione, effetti secondari

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