Canine eosinophilic granuloma of the digits treated with prednisolone and chlorambucil

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Background – Canine eosinophilic granuloma (CEG) is an uncommon disease. Lesions are typically located in the oral cavity and other cutaneous sites, but are rarely reported to affect the digits. The majority of cases are treated with prednisolone as a monotherapy; alternative treatment options include corticosteroids administered in combination with azathioprine, antihistamines, electrochemotherapy with bleomycin, and surgical resection. Neither chlorambucil nor laser previously have been reported as treatments.

Objectives – To describe an alternative therapy for treatment of CEG; using chlorambucil in combination with prednisolone for those cases that fail to respond to prednisolone alone. The new treatment was chosen according to good clinical practice and after owner consent.

Animals – Two client owned dogs.

Methods – One case was initially treated with carbon dioxide laser to debulk the lesions. Both cases were treated with a combination of oral prednisolone and chlorambucil.

Results – Both dogs experienced rapid resolution of lesions with prednisolone and chlorambucil therapy. Case 1 remained in remission three months after withdrawing medication. Case 2 experienced relapse 10 weeks after discontinuing therapy but was well controlled on maintenance prednisolone with chlorambucil at low, well tolerated doses.

Conclusions and clinical importance – Although CEG appears to be an uncommon disease, it should be included as a differential diagnosis for dermal, nodular lesions affecting the digits. Chlorambucil appears to be an effective and well tolerated prednisolone sparing agent for treatment of CEG. Carbon dioxide laser ablation appears to be an effective method of debunking CEGs.

Introduction
Canine eosinophilic granuloma (CEG) is an uncommon skin disease. The typical clinical presentation includes papules, nodules and/or plaques most frequently located in the oral cavity and infrequently involving other cutaneous sites such as the nasal planum, ventral abdomen, thorax, metatarsus, prepuce, flank, digit, eyelid, external ear canal and cheek region. 

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Case 1
A 3.5-year-old, spayed female, 26 kg boxer dog presented with a 6 week history of dermal nodular lesions affecting the feet, face and pinnae. The owner reported partial reduction in the size of the lesions subsequent to administration of prednisolone at a dosage of 1 mg/kg, but the drug was withdrawn by the owner as they were unaware and intolerant of prednisolone adverse effects. On clinical evaluation, there were six, firm, nonpruritic, erythematous, alopecic, ulcerated nodules to plaques, measuring 0.4–1.5 cm in diameter affecting all four paws (Figure 1a). Two nodular lesions with ulceration measuring 8 mm and 20 mm (respectively) were located on the plantomedial aspect of digit IV of the right hind paw (Figure 1b).

Fine needle aspirates of multiple cutaneous nodules revealed macrophages and degenerate neutrophils with occasional intracellular cocci. A complete blood count (CBC), serum biochemistry and urinalysis revealed no abnormalities. One 8 mm and three 6 mm skin biopsy specimens were collected from several nodules for histological evaluation.

Histopathological examination revealed a diffuse, interstitial, eosinophilic dermatitis with multinucleated giant cells and occasional eosinophilic flame figures (Figure 2). In one section, a modest population of large, irregular, round cells accompanied the eosinophilic dermatitis. Toluidine blue staining suggested that mast cells were more likely reactive than neoplastic. Subsequent immunohistochemical (IHC) evaluation (CD3, CD79a and CD18) revealed that c.30% of the large irregular round cells were CD3 positive. The provisional diagnosis was CEG with reactive lymphoid infiltrate.
Oral prednisolone was instituted at a dosage of 1.5 mg/kg/day for 10 days and then tapered by 25% of the induction dose every 14 days to 0.8 mg/kg/day. Subsequent to dose reduction, several new lesions developed. Oral chlorambucil was initiated at 2.25 mg/m² twice daily (for 2 weeks, reduced to once daily thereafter) in conjunction with prednisolone 0.8 mg/kg once daily and oral amoxicillin-clavulanate (12.5 mg/kg twice daily for 28 days). After approximately 7 weeks of combination treatment, the lesions had improved markedly and the prednisolone dose was tapered to alternate day therapy. After approximately 20 weeks of treatment, chlorambucil was withdrawn and prednisolone continued at 0.5 mg/kg/day therapy and withdrawn after 42 weeks of treatment. There was no relapse for 3 months after all medication had been withdrawn.

**Case 2**

A 10-year-old, intact female, 32.6 kg boxer dog presented with a 5 month history of nodular, ulcerated lesions affecting all four paws. The referring veterinarian reported resolution of the hind paw lesions with clindamycin administration. The fore paw lesions, however, continued to enlarge despite multiple treatments (amoxicillin-clavulanate, clindamycin, meloxicam and prednisolone). On clinical evaluation there were two, firm, nonpruritic, erythematous and alopecic, ulcerated nodules measuring 8 mm and 20 mm located on the plantomedial aspect of the digit IV of the right hind paw.

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concurrently with chlorambucil (1.95 mg/m²/day) for the following 2 weeks. Oral antibiotics were replaced with topical povidone iodine treatment 2 weeks after starting prednisolone therapy. At this time, the digital pads had assumed normal anatomic conformation with minimal swelling and a small area of moist erythematous granulation tissue remained in both wounds. The prednisolone dose was reduced by 25% every 2 weeks, and both the chlorambucil and prednisolone were discontinued after 8 weeks of treatment.

Approximately 10 weeks after withdrawal of medications, a small area of erosion and erythema developed on the right hind paw. The prednisolone/chlorambucil combination was restarted by the referring veterinarian. This led to remission within 1 week; 8 weeks after restarting therapy the dog was maintained with prednisolone (0.5 mg/kg every other day, eod), alternating with chlorambucil (1.95 mg/m² eod) with no relapse.

**Discussion**

There are few reports of CEGs involving the digits and they have not been described previously in boxer dogs. Previous reports described solitary lesions affecting one paw in an Irish setter,2 Labrador retriever3 and Labrador retriever mix.16 This disease should be included in the differential diagnoses list of dogs presenting with firm, non-pruritic, erythematous, alopecic and ulcerated nodules to plaques on the digits. Differential diagnoses for nodular skin lesions with an eosinophilic infiltrate also include mast cell tumour, insect/arthropod bite reaction, foreign body reaction, fungal infection and aberrant parasitic migration.8

Histopathology and special stains (Ziehl Neelsen and periodic acid Schiff) were performed to rule out infectious aetiologies prior to presentation. Histopathology was repeated followed by IHC, in both instances, to rule out neoplasia. In Case 1 mast cell and lymphoid infiltrates were suspected to be reactive (not neoplastic); the possibility of epitheliotropic T-cell lymphoma could not be excluded. However, resolution with treatment and lack of relapse upon discontinuation rules out this possibility.

CEG lesions are typically managed with anti-inflammatory dosages of oral glucocorticoids7 and approximately 78% are responsive to this treatment.10,13 The majority of reported cases have used corticosteroid monotherapy to achieve successful control. With large CEG lesions, surgical debulking has been performed.8,11,15 Glucocorticoids may be combined with oral azathioprine for refractory cases.4,9,13 Reported treatments for CEG may also include chlorpheniramine and electrochemotherapy with bleomycin.8,11,15 To the best of the authors’ knowledge, chlorambucil or laser ablation for dogs with EG has not been reported previously. These appeared to be viable options for prednisolone sparing and improving comfort quickly.

Advantages associated with CO₂ laser (compared to cold steel surgery) include improved haemostasis, precision, noncontact dissection (reducing intraoperative wound contamination by tumour cells), fewer instruments at the site of operation, reduced postoperative pain through nerve capping and minimizing trauma to surrounding tissues.17–19 The average zone of thermal necrosis after laser incision in soft tissues is 0.6 mm.20

Prednisolone is a glucocorticoid that alters transcription of DNA, modifying cellular metabolism and resulting in anti-inflammatory, immunosuppressive and antifibrotic effects,21 adverse effects can be numerous and unacceptable.22 Combination with additional immunosuppressive medications can lower the prednisolone dose into a tolerated range (prednisolone sparing).23

Chlorambucil is a cell cycle nonspecific alkylating antineoplastic / immunosuppressive agent. Therapeutic indications in dogs include lymphocytic leukaemia, multiple myeloma and ovarian adenocarcinoma.24 It has previously been shown to be an effective prednisolone sparing agent23 and has been used in humans with multifocal EGs.25 Chlorambucil was chosen as an alternative to ciclosporin due to financial constraints. As both cases were large dogs, ciclosporin was prohibitively expensive, whereas chlorambucil was not.

Case 1 showed significant muscle wastage, polyuria/polydipsia (PU/PUD) and behavioural changes at high doses (>1.5 mg/kg) of prednisolone so it was not possible...
to see if the condition would have resolved had it been treated with prednisolone monotherapy at a higher dose (2 mg/kg/day). In Case 2, open wound location (to heal by secondary intention), in addition to expected owner noncompliance (keeping wounds clean), necessitated prophylactic use of amoxicillin-clavulanate. Meloxicam was provided for analgesic/anti-inflammatory properties, again, due to the location of wounds, on the weight bearing aspect of paws. The authors do not condone routine use of prophylactic systemic antibiotics after surgery.

Chlorambucil was an effective adjunctive immunosuppressive agent for these CEGs, and may be considered for cases that don’t respond to prednisolone monotherapy, or cannot tolerate the adverse effects of high dose prednisolone. The risk of myelosuppression associated with chlorambucil necessitates CBC monitoring; initially frequently (0, 1, 2, 4, 8 and 12 weeks), then every 3–6 months thereafter.24 It is not possible to make conclusive predictions regarding the broader population due to the small number of cases discussed. With the previously mentioned benefits and minimal postoperative discomfort in Case 2, laser appears to be a viable alternative to surgical resection of these masses.

As the underlying aetiology of these lesions is still unclear, further research is required to allow more targeted treatment recommendations for this condition.

Acknowledgements
We would like to thank John Mackie (Vepalabs) and Brett Stone (QML Pathology Vetnostics Service) for assistance with histopathology.

References

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Methoden – Ein Fall wurde zunächst mit Carbondioxid Laser behandelt, um die Veränderungen zu verkleinern. Beide Fälle wurden mit einer Kombination von Prednisolon per os und Chlorambucil behandelt.

Ergebnisse – Bei beiden Hunden heilten die Veränderungen mit einer Therapie von Prednisolon und Chlorambucil rasch ab. Fall 1 blieb drei Monate nach Beendigung der Medikamente in Remission. Fall 2 zeigte 10 Wochen nach Absetzen der Therapie ein Wiederauftreten der Veränderungen, die die Zehen betrafen, blieb aber bei niedriger dosierter, gut verträglicher Dosierung von Prednisolon und Chlorambucil gut kontrolliert.

Schlussfolgerungen und klinische Bedeutung – Obwohl das CEG scheinbar eine seltene Erkrankung darstellt, sollte es in der Differentialdiagnose für dermale, noduläre Veränderungen, die die Zehen betreffen, nicht fehlen.

Conclusions et importance clinique – Aunque CEG es una enfermedad poco común, debido ser incluida como un diagnóstico diferencial para lesiones nodulares derrhicas que afectan a los dígitos. El clorambucilo parece ser un agente bien tolerado para disminuir la dosis de prednisolona en el tratamiento de la CEG. La ablación con láser de dióxido de carbono parece ser un método eficaz de reducción del volumen de CEGs.

Zusammenfassung


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要約

背景 – イヌの好酸球性肉芽腫(CEG)は稀な疾患である。典型的な変化は口腔内および他の皮膚の部位に認められるが、趾間が罹患すると報告されたことはほとんどない。大部分の症例はプレドニゾロンを単独で使用して治療しており、代替療法の選択肢はアザチオプリンと副腎皮質ステロイドの併用、抗ヒスタミン剤、ブレオマイシンなどの電気化学療法ならびに外科的な切除が含まれる。本アクロプラジアレーザーはこれまで治療として報告されたことがない。

目的 – プレドニゾロン単独治療の反応の乏しい症例に対して、プレドニゾロンとクロラムブシルの併用によるCEGの治療のための代替療法を解説することである。新しい治療法はおよび飼い主の同意のもとに医療品の臨床試験実施の基準に基づいて選択された。

供与動物 – 2頭の飼い犬

Resumen

Introducción – el granuloma eosinofílico canino (CEG) es una enfermedad poco frecuente. Las lesiones se encuentran normalmente en la cavidad oral y otros sitios cutáneos, pero rara vez son reportados afectando a los dígitos. La mayoría de los casos son tratados con prednisolona como monoterapia; las opciones alternativas de tratamiento incluyen corticosteroides administrados en combinación con azatioprina, antihistamínicos, electroquimioterapia con bleomicina y resección quirúrgica. Ni clorambucilo ni láser han sido previamente descritos como tratamientos.

Objetivos – describir una terapia alternativa para el tratamiento de CEG, usando clorambucilo en combinación con prednisolona para aquellos casos que no responden a la prednisolona sola. El nuevo tratamiento se eligió siguiendo buenas prácticas clínicas y después del consentimiento del propietario.

Animales – Dos perros de propietarios privados.

Métodos – Un caso fue tratado inicialmente con láser de dióxido de carbono para reducir el volumen de las lesiones. Ambos casos fueron tratados con una combinación de prednisolona oral y clorambucilo.

Resultados – Ambos perros experimentaron una rápida resolución de las lesiones con el tratamiento con prednisolona y clorambucilo. El caso 1 se mantuvo en remisión tres meses después de la retirada de la medición. El caso 2 experimentó una recaída 10 semanas después de la interrupción del tratamiento, pero fue bien controlado con dosis baja y bien tolerada de mantenimiento de prednisolona con clorambucilo.

Conclusiones e importancia clínica – Aunque CEG es una enfermedad poco común, debe ser incluida como un diagnóstico diferencial para lesiones nodulares derrhicas que afectan a los dígitos. El clorambucilo parece ser un agente bien tolerado para disminuir la dosis de prednisolona en el tratamiento de la CEG. La ablación con láser de dióxido de carbono parece ser un método eficaz de reducción del volumen de CEGs.
方法 — 1例では元々は病変の減容積を目的に炭酸ガスレーザーで治療されていた。両症例ともに経口ブドニゾロンおよびクロラムフェニールの併用で治療された。

結果 — 両例の1例で「ブドニゾロンとクロラムフェニール」の治療で病変の急速な消失が認められた。症例1は薬剤終了後3ヶ月後に覚解を保っていた。症例2では治療中止後10週間で再発が認められたが、維持量のブドニゾロンと低用量で「寛容」できる用量のクロラムフェニールで「良好に管理されている」。

結論および臨床的な重要性 — CEGは稀な疾患だが、臨床の皮膚の結節性病変に対する鑑別診断に含めるべきである。クロラムフェニールは効果的でよく覚察され、CEGの治療としてブドニゾロンを減量するために使用できる薬剤である。炭酸ガスレーザーの使用はCEGの減容積の効果的な方法であると思われる。

の要 — 犬嗜酸性肉芽腫症(CEG)は一種の稀な病気で、典型的に口腔および皮肤に発症する。しかし、少数例では他の部位に発症する。治療方法としてステロイド、抗生剤、免疫抑制剤、手術が挙げられる。治療の対応は症例により異なる。症例1はブドニゾロンの併用で覚解を保つことができたが、症例2は薬物療法が不十分で再発を繰り返していた。CEGの治療法は個別に選択されるべきである。

結論 — CEGは犬の稀な疾病で、治療法は個別に選択されるべきである。治療の目的は病状の寛容化と再発の防止である。治療の選択は症例により異なるので、適切な診断と治療が必要である。