

Aus dem klinischen Department für Kleintiere und Pferde
der Veterinärmedizinischen Universität Wien

Klinisches Zentrum für Kleintiere
(Leitung: Ass. Prof. Dr. med. vet. Britta Vidoni)

**Treatment of a non-responsive eosinophilic vasculitis in a dog with
low-dose radiotherapy and Oclacitinib: a case report**

Diplomarbeit

Veterinärmedizinische Universität Wien

vorgelegt von

Vera Sauter

Wien, im Mai 2025

Betreuerin: Ao.Univ.-Prof. Dr.med.vet. Miriam Kleiter, Dipl.ACVR-RO, Dipl.ECVIM-CA
(Oncol)

Klinisches Zentrum für Kleintiere (Bereich Radioonkologie und Nuklearmedizin
der Internen Medizin Kleintiere)

Klinisches Department für Kleintiere und Pferde

Veterinärmedizinische Universität Wien

Dr. med. vet Constanze Hartmann

Forschungsservice

Universität für Bodenkultur Wien

BegutachterIn: Dr. med. vet. Lucia Panakova, Dipl.ECVD,

Klinisches Zentrum für Kleintiere (Bereich Dermatologie der Internen Medizin
Kleintiere)

Klinisches Department für Kleintiere und Pferde

Veterinärmedizinische Universität Wien

Eigenständigkeitserklärung

Hiermit erkläre ich, dass ich die vorgelegte Arbeit selbstständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe. Alle übernommenen Textstellen aus fremden Quellen wurden kenntlich gemacht.

Ich habe die entscheidenden Arbeiten selbst durchgeführt und alle zuarbeitend Tätigen mit ihrem Beitrag zur Arbeit angeführt.

Die vorliegende Arbeit wurde nicht an anderer Stelle eingereicht oder veröffentlicht.

Wien, den 23.05.2025

Vera Sauter

KEY WORDS

irradiation, oral, eosinophilic vasculitis, canine, oclacitinib

ABSTRACT (Deutsch)

Eine eosinophile Vaskulitis ist ein entzündlicher Prozess in der Gefäßwand, der zu Blutungen, Ischämie und Nekrose im umliegenden Gewebe führt. Zur Behandlung eosinophiler Erkrankungen ist es notwendig, die zugrunde liegende Ursache zu identifizieren und zu beseitigen. Kann keine Ursache gefunden werden, erfolgt eine symptomatische Behandlung mit Immunsuppressiva wie Glukokortikoiden, Ciclosporin und Azathioprin. Häufig sprechen eosinophile Läsionen jedoch nicht auf die Therapie an oder treten nach Behandlungsende wieder auf.

In diesem Fallbericht wurde bei einer sechs Jahre alten kastrierten Mischlingshündin eine eosinophile Vaskulitis in der caudalen Maulhöhle diagnostiziert. Verschiedene Therapieansätze mit diversen Immunsuppressiva, Antibiotika und NSAIDs führten nur zu vorübergehenden Verbesserungen des klinischen Zustands. Daher wurde eine niedrig dosierte Entzündungsbestrahlung vorgeschlagen, da diese immunmodulierende und entzündungshemmende Effekte erzielen kann und bereits Erfolge in der Bestrahlung anderer chronisch-entzündlicher Erkrankungen bei Kleintieren wie der caninen Osteoarthritis, verzeichnet wurden. Auch in der Humanmedizin ist die Bestrahlung mit geringen Dosen bereits eine etablierte Therapiemethode zur Behandlung chronisch-entzündlicher Erkrankungen. Die Entzündungsbestrahlung erfolgte mit einer Gesamtdosis von 12 Gy über vier Tage mit einer Einzelfraktion von 3 Gy.

Zusätzlich zur Entzündungsbestrahlung wurde die Patientin für drei Monate mit Oclacitinib behandelt. Die Kombinationstherapie führte zu einer raschen klinischen Verbesserung mit Rückbildung der intraoralen eosinophilen Läsionen. Diese klinische Remission hielt über den Beobachtungszeitraum von acht Jahren ohne erneuten Rückfall an. Eine Entzündungsbestrahlungstherapie stellt in Kombination mit Oclacitinib einen vielversprechenden Ansatz zur Behandlung einer therapieresistenten eosinophilen Vaskulitis dar. Weitere Studien sind indiziert, um das Therapieergebnis zu bestätigen und zu evaluieren, ob eine Entzündungsbestrahlung oder Oclacitinib als Monotherapie einen vergleichbaren therapeutischen Effekt erzielen können wie ihre Kombination.

ABSTRACT (Englisch)

An eosinophilic vasculitis is an inflammatory process in the vessel wall that leads to bleeding, ischemia, and necrosis in the surrounding tissue. For the treatment of eosinophilic diseases, it is necessary to identify and eliminate the underlying cause. If no cause can be found, symptomatic treatment with immunosuppressants such as glucocorticoids, cyclosporine, and azathioprine is administered. However, eosinophilic lesions often do not respond to therapy or recur after treatment has ended.

In this case report, eosinophilic vasculitis was diagnosed in the caudal oral cavity of a six-year-old spayed female mixed-breed dog. Various treatment approaches using different immunosuppressants, antibiotics, and NSAIDs only led to temporary improvements in the clinical condition. Therefore, low-dose anti-inflammatory radiotherapy was proposed, as it can achieve immunomodulatory and anti-inflammatory effects and has already shown success in the irradiation of other chronic inflammatory diseases in small animals, such as canine osteoarthritis. In human medicine as well, low-dose radiation therapy is an established method for treating chronic inflammatory diseases. The anti-inflammatory radiotherapy was administered at a total dose of 12 Gy over four days, with a single fraction dose of 3 Gy.

In addition to radiotherapy, the patient was treated with oclacitinib for three months. The combination therapy led to a rapid clinical improvement with regression of the intraoral eosinophilic lesions. This clinical remission persisted over an observation period of eight years without recurrence. Anti-inflammatory radiotherapy in combination with oclacitinib represents a promising approach for the treatment of therapy-resistant eosinophilic vasculitis. Further studies are warranted to confirm the therapeutic outcome and to evaluate whether radiotherapy or oclacitinib as monotherapy can achieve a comparable therapeutic effect to their combination.

Table of contents

ABSTRACT (DEUTSCH)	5
ABSTRACT (ENGLISCH)	6
1. LIST OF ABBREVIATIONS	9
2. INTRODUCTION.....	1
2.1. CUTANEOUS VASCULITIS	1
2.1.1. <i>Definition</i>	1
2.1.2. <i>Classification</i>	1
2.1.3. <i>Causes and genetic predispositions</i>	2
2.1.4. <i>Clinical Features</i>	2
2.1.5. <i>Differential diagnosis</i>	2
2.1.6. <i>Diagnosis</i>	3
2.1.7. <i>Therapy</i>	3
2.1.8. <i>Prognosis</i>	4
2.2. OCLACITINIB.....	4
2.3. EOSINOPHIL GRANULOCYTES	4
2.4. LOW-DOSE RADIATION THERAPY	5
2.4.1. <i>Definition</i>	5
2.4.2. <i>History of radiation treatment in animals</i>	6
3. CASE REPORT.....	8
3.1. CLINICAL HISTORY	8
3.2. CLINICAL FINDINGS	9
3.3. IRRADIATION THERAPY	12
3.4. FOLLOW UP AND OUTCOME.....	13
4. DISCUSSION	14
5. CONCLUSION	21
6. REFERENCES.....	22

7.	LIST OF FIGURES.....	27
----	----------------------	----

1. List of abbreviations

JAK	janus kinase
IL	interleukin
GM-CSF	granulocyte-macrophage colony-stimulating factor
LDRT	low-dose radiation therapy
OA	osteoarthritis
LDR	low-dose radiation
MUO	meningoencephalitis of unknown origin
CBC	complete blood count
EGC	eosinophilic granuloma complex
NF- κ B	nuclear factor kappa B
iNOS	nitric oxide synthase
TGF- β 1	transforming growth-factor-beta 1
ROS	reactive oxygen species
NO	nitric oxide

2. Introduction

2.1. Cutaneous vasculitis

2.1.1. Definition

Cutaneous vasculitis is an immune-mediated inflammatory disease affecting the blood vessels in the skin and leading to vessel wall damage (1,2). Through lesions in the vascular wall blood leaks into the surrounding tissue resulting in tissue ischemia and necrosis (3). It is to mention that the term “vasculitis” does not describe a definitive diagnosis, but a cutaneous reaction pattern that is associated with multiple causes (4).

2.1.2. Classification

Cutaneous vasculitis can be classified based on the size of the affected vessels or depending on the localisation, further it can be histopathologically divided into leukocytoclastic vasculitis and non-leukocytoclastic vasculitis. Small Vessel Vasculitis is the most common type of vasculitis in small animals and involves the capillaries, venules and arterioles in the superficial dermis (2). Medium Vessel Vasculitis affects medium-sized arteries and veins in the deep dermis or subcutis while Large Vessel Vasculitis involves larger arteries and veins in subcutaneous or deeper tissue (2). However, the latter occurs rarely in small animals (2). The classification into local or systemic vasculitis is not just about the location of the affected blood vessels, but rather about whether the inflammation is limited to the skin or involves multiple organ systems (4). The distinction between non-leukocytoclastic and leukocytoclastic vasculitis is mainly histopathological (1). Leukocytoclastic vasculitis represents the most common form of cutaneous vasculitis in small animals and is characterized by a neutrophilic infiltration of vessel walls, leading to nuclear fragmentation (1). Histologically neutrophil infiltration is visible around and within the vessels, as well as leukocytoclasia and deposition of fibrin and necrotic debris in the vascular walls, making them appear swollen (1). In contrary to that non-leukocytoclastic vasculitis lacks the leukocytoclasia of the neutrophils and instead other inflammatory cells such as eosinophils and lymphocytes predominate (1). Depending on the predominant cell type non-leukocytoclastic vasculitis can be further divided into eosinophilic vasculitis and lymphoplasmacytic vasculitis (1).

2.1.3. Causes and genetic predispositions

Cutaneous vasculitis can be triggered by a variety of factors including infections of bacterial, viral or parasitic origin, insect or tick bites including the transmission of pathogens, food allergies, reactions to drugs or vaccinations, neoplastic diseases such as mast cell tumours and auto-immune diseases e.g. lupus erythematosus (1,4). Eosinophilic vasculitis has been especially associated with arthropod reactions, canine eosinophilic dermatitis, food hypersensitivity and mast cell tumours (4). Some familial forms of vasculitis have been observed in breeds such as the Scottish Terrier, Shar-Pei, Greyhound, Saint Bernard, German Shepard and Jack Russell Terrier, suggesting a hereditary component in immune dysregulation (1,4). Idiopathic cutaneous vasculitis refers to cases where no clear underlying cause can be identified, despite thorough diagnostic evaluation (1).

2.1.4. Clinical Features

Symptoms vary depending on the severity and the affected blood vessels. Cutaneous signs of acute or severe vasculitis can be palpable purpura, erythematous to purpuric plaques, haemorrhagic bullae, eschar, crateriform ulcers, pitting oedematous areas and occasionally acrocyanosis (4). Lesions typically involve the extremities, pinnae, lips, tail, scrotum and oral mucosa (4). These lesions can also follow vascular pathways and will then have a linear pattern (4). They also may or may not be painful (4). Systemic symptoms further include fever, apathy and weight loss (1,4).

2.1.5. Differential diagnosis

The differential diagnosis is variable depending on what types of lesions predominate (4). Differentially, sepsis, disseminated intravascular coagulation, cryoglobulinemia, cryofibrinogenemia, systemic lupus erythematosus, lymphoreticular neoplasia, subepidermal bullous diseases, burns, dermatophytosis, Demodex, dermatomyositis, cold agglutinin disease, frostbite, Erysipelothrix rhusiopathiae infections, and Rocky Mountain spotted fever are considered (1,4).

2.1.6. Diagnosis

To effectively diagnose cutaneous vasculitis a combination of examinations including anamnesis, clinical examination and dermatological examination, blood tests, urine analysis, elimination diet and histopathology are necessary (1,2). To determine the cause of any vasculitis a thorough drug and vaccine history is also indicated as lesions often develop two to six months following an inciting vaccination (4). Vector-borne infectious diseases including babesiosis, ehrlichiosis, anaplasmosis and bartonellosis as well as *Rickettsia rickettsii*, *Borrelia burgdorferi* and *Leishmania infantum* should be tested for (4). Identification for these infections does not prove they caused the vasculitis but would be suspicious and warrant appropriate therapy (4).

Histopathology findings vary depending on which vascular syndrome is present, age of the lesion biopsied related to the vascular damage and secondary infections (4). The vascular lesions may be marked or mild and associated with different types of inflammatory cells (4). Considering the variation and subtle vascular changes or the follicular, dermal or epidermal changes suggestive of hypoxia it is important that the clinician takes extra care in submitting biopsy samples (4).

2.1.7. Therapy

The clinical course varies depending on the vasculitis syndrome and source (4). The most important way to treat cutaneous vasculitis is to identify and eliminate the underlying cause (e.g. discontinue suspected drugs or food) (1). If no underlying trigger can be identified therapy with immunosuppressants such as glucocorticoids, ciclosporin and azathioprine should be considered (1,4). In difficult cases, a combination of three or more drugs can be used e.g. glucocorticoid, azathioprine, cyclosporine and pentoxifylline can be all used together (4). Mild cases can be treated with hemorheological agents (e.g. pentoxifylline) and doxycycline (4). Old reports have also shown that sulfones may be effective (4). Large doses of Vitamin E can be a useful adjunctive therapy, as may tetracycline and niacinamide (4). Further it is important to treat skin lesions and therefore prevent secondary infections. Sometimes therapy can be stopped after four to six months but some patients require long-term maintenance therapy with lower drug doses and reduced frequency of administration (4).

2.1.8. Prognosis

The prognosis of cutaneous vasculitis depends on the underlying cause and response to treatment (4). Idiopathic cases can be chronic and recurrent (4). Therefore, early intervention is essential to improve the outcome and quality of life for the patient (4).

2.2. Oclacitinib

Oclacitinib is an immunomodulatory agent with anti-inflammatory, anti-allergic and anti-pruritic characteristics. It is normally used to treat atopic dermatitis and pruritus associated allergic dermatitis in dogs (5). It selectively inhibits the enzyme Janus kinase (JAK) 1 which is responsible for the activation of pro-inflammatory, pro-allergenic and pruritus-causing agents (5). This includes IL-2, IL-4, IL-6, IL-13 and IL-13 and to a lesser extent JAK 2, JAK 3, erythropoietin, GM-CSF, IL-12 and IL-23 (5).

2.3. Eosinophil granulocytes

Eosinophils are multifunctional granular leukocytes involved in the pathogenesis of a wide variety of diseases including asthma, helminth infections, and rare hypereosinophilic syndromes (6). They are characterised by their bilobed nucleus and the presence of granules in their cytoplasm that stain with eosin red (7). Eosinophilic granulocytes develop in the bone marrow under the influence of several transcription factors including GATA-binding factor 1 and cytokines such as interleukin 3 and 5 (IL-3 and IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (6). Primed by these factors, eosinophils exhibit increased susceptibility to stimulating factors including cytokines and inflammatory mediators (8). In healthy individuals, the vast majority of eosinophils (> 90%) reside in the tissue, where they can be found in the gastrointestinal tract, spleen, lymph nodes, thymus, mammary glands and uterus, in disease states however eosinophils migrate along chemokine gradients to sites of inflammation (6).

Eosinophils defend against invading pathogens intracellularly by phagocytosis or by extracellular killing mechanisms such as degranulation, eosinophil extracellular traps and respiratory burst (8). They are also known to play a role in immune regulation for example by activating basophils, mast cells and neutrophils as well as dendritic cells (8). Eosinophils and their secretory products may also play other essential roles in metabolism, fat deposition and

glucose homeostasis, tissue remodelling and development, liver and muscle repair, neuronal regulation, epithelial and microbiome regulation and are further known to have antiparasitic functions (9).

While circulating eosinophils experience a short half-life of approximately 8-18 hours, eosinophils residing in tissue have a prolonged life span of up to 14 days (8). In the absence of external survival-prolonging stimuli such as GM-CSF, IL-5 or IL-3 programmed spontaneous apoptosis is induced within a few days (8). Failure of apoptotic clearance or excessive recruitment of eosinophils is frequently observed in chronic inflammatory diseases (8).

For treatment of inflammatory eosinophilic diseases, it is important to rule out the main causes and possible triggers. If no cause is confirmed, the animal is treated symptomatically (3). To date, several different treatments are used for eosinophil-associated inflammatory diseases including glucocorticoids, cyclosporine, cetirizine and agents against IL-5, IL-5R α , and IL-13 (8).

2.4. Low-dose radiation therapy

2.4.1. Definition

In veterinary and human medicine, a distinction is made between high-dose irradiation for cancer treatment and low-dose radiation (LDRT) for treatment of non-neoplastic inflammatory conditions. Radiotherapy against cancer can be used as a curative treatment or as a palliative treatment. The aim of a curative treatment is to locally control a tumour long-term (10). Therefore, radiation protocols are more aggressive and use a high total dose of 45-52 Gy (10). Single fractions of about 3 Gy are typically administered daily over a period of approximately three and a half weeks (10). In contrast to that, palliative radiation treatment is not intended for long-term tumour control but rather for maintaining or improving quality of life and to control the tumour short-term (10). As a result, palliative radiation therapy is typically used in advanced stages of the disease or if coexisting conditions affect treatment options (10). Compared to curative treatment protocols, palliative treatment is less aggressive and total doses of 20-36 Gy are used (10). It furthermore consists of fewer single fractions, usually three to six, that are administered either daily or once to twice a week. (10). For LDRT usually total doses of 6-12 Gy are used, while the fractionation is individually determined by the veterinarian. LDRT is known for its anti-inflammatory and immunomodulating effect which can be used in the treatment of chronic inflammatory diseases (11).

Immune-related diseases such as rheumatism, systemic lupus erythematosus and collagen-induced arthritis in mouse models have been successfully treated with LDRT. In Germany approximately one-third of all human radiation therapy treatments are for benign diseases and inflammatory conditions (12,13,14,15). In small animals LDRT is not yet established as a routine treatment option. However, with the increase of veterinary institutions offering radiotherapy more veterinarians consider LDRT as an alternative treatment option for chronic inflammatory diseases and immune-mediated conditions that are non-responsive to drugs.

2.4.2. History of radiation treatment in animals

As early as in 1958, Alois Pommer, professor for radiology at the University of Veterinary Medicine in Vienna, reported on the radiotherapeutic treatment of acute and chronic joint diseases (16). He pointed out that this symptomatic treatment might have an effect on the inflammatory process in the joint (16). In addition to its analgetic effect and improvement of joint function, he also described a reduction of oedema (16). He further studied the effect of radiotherapy on a variety of skin diseases in small animals. Depending on the pathology itself, its depth and the cell types involved he chose different radiation protocols to treat the condition, mainly using comparably low doses (17). While treating diseases such as eczema, otitis externa, acne, seborrhoea, sycosis vulgaris and acanthosis nigricans, Pommer discovered that radiotherapy has an anti-inflammatory impact on the skin and further inhibits the skin glands functioning (17). The anti-pruritic effect of the radiotherapy further caused a quicker healing of the affected skin (16). In 2017 Eberle published an article, about the use of radiation therapy in the pain management of dogs and cats (18). She described that besides its anti-inflammatory effect LDRT reduces pain and therefore is able to significantly improve the quality of life for the patient (18). The primary cause of pain in degenerative joint conditions is the local acidosis which develops over the course of the disease (18,19). LDRT manages to shift the pH into a more alkaline milieu (18,19). This analgesic effect can then last up to six to nine months and normally occurs about four to six weeks after completion of the radiation treatment (18). As indicators for LDRT Eberle lists osteoarthritis (OA), osteochondrodysplasia of the Scottish fold cat and neoplasia (18). Other small animal diseases that were irradiated to study the effect of low-dose radiation (LDR) were the meningoencephalitis of unknown origin (MUO) in dogs and feline idiopathic cystitis and feline chronic enteropathies in cats. At the American College of Veterinary Radiology Congress in 2023 Gieger et al. presented their studies about the radiation treatment of cats suffering from enteropathy-associated T cell lymphoma or

inflammatory bowel disease (20). They chose a radiation protocol of 4 x 2 Gy and noticed a significant clinical improvement in most cats (20). In 2024 Kendall et al. published a study that proved that LDR vastly improves hard-to-treat feline idiopathic cystitis in male cats (21).

To the best of our knowledge LDRT in combination with oclacitinib has not been used before to treat localized eosinophilic vasculitis in small animals. Therefore, in this case report LDRT and oclacitinib are presented as a new therapy approach to treat non-responsive localised mucosal eosinophilic vasculitis in a dog.

3. Case Report

3.1. Clinical History

In May 2015, a four-year old mixed-breed spayed female dog, with a body weight of 10 kg was presented at the small animal clinic of the Veterinary University of Vienna. The dog was adopted from a Slovakian animal shelter in 2012. Therefore, nothing is known about the patient's medical history prior the adoption. Immediately after adoption, giardiasis was treated, but otherwise the patient was healthy. Until April 2013, the dog has been regularly dewormed and vaccinated, but no other medication was used.

Between 2013 and 2015 the patient experienced several episodes of pain localized in the orofacial area. Typical signs of pain were squeaking while chewing on cardboard, stepping back suddenly after yawning and a change in eating behaviour. Diagnostic work-up for the pain episodes included haematology and biochemistry profiles, radiographs of the mandibular joints, mandibles and maxillae, a CT scan of the head and neck and a muscle biopsy of the masticatory muscle to localize the source of the pain and its underlying cause. However, no abnormalities were detected. The patient was then treated symptomatically with NSAIDs and antibiotics. Antibiotic therapy included amoxicillin and acidum clavulanicum (12.5 mg/kg/bid, p. o., Clavaseptin® 250 mg ad us. vet. dividable tablets, VETOQUINOL S.A. France) for seven days in combination with Cimicoxib (2 mg/kg/sid, p. o., Cimalgex® 30 mg ad us. vet. dividable tablets, VETPQUINOL S.A., France) for five days, which led to a temporary significant improvement of the symptoms. After this therapy stopped the patient relapsed and a monotherapy with carprofen (4 mg/kg/sid, p. o., Rimadyl® 100 mg ad us. vet. tablets, Zoetis Deutschland GmbH, Germany) for four weeks was prescribed. Shortly after therapy was stopped, the patient was again showing signs of pain and amoxicillin and acidum clavulanicum (12.5 mg/kg/bid, p. o., Kesium® 200 mg/50 mg ad us. vet. dividable tablet for dogs, Biokema SA, Swiss) was given for ten days. This again led to a temporary improvement in the patient, but it repeatedly relapsed. The examinations up to this point had ruled out some suspected diagnoses such as chewing muscle myositis, otitis media or tooth fractures. but no diagnosis could be made. At the time of presentation in May 2015 the patient was again showing an episode of pain with clinical signs such as squeaking, retreating after yawning, and difficulty chewing.

3.2. Clinical Findings

The clinical examination in May 2015 revealed pain when opening the oral cavity. The oral cavity could not be examined while the patient was awake. The blood count was normal except for a slight eosinophilia. Radiography of the mandibular joints and cervical spine, and otoscopy were unremarkable. Under general anaesthesia, two symmetrical ulcerated plaques measuring 1 cm x 2.5 cm were found in the tonsillar region (Fig. 1). A bacterial stomatitis was considered as a differential diagnosis and biopsies for histopathologic examination and bacterial culture were taken from these mucosal lesions. Bacteriological results revealed high-grade contamination with α -haemolytic streptococci and *Pasteurella multocida*. Histopathological examination showed dense eosinophilic infiltration and chronic granulation tissue with evidence of vasculitis (Fig. 3).



Figure 1a



Figure 1b

Figure 1 Eosinophilic plaques in the oral cavity, 1a before treatment with antibiotics, 1b after treatment with antibiotics.

The diagnosis based on these findings was then oral eosinophilic plaques with eosinophilic vasculitis. Treatment included clindamycin (5.5 mg/kg/bid, p. o., Antirobe® 25 mg ad us. vet., capsules for dogs, Zoetis Deutschland GmbH, Germany) for three weeks, meloxicam (0.1 mg/kg/sid, p. o., Metacam® 1.5 mg/ml ad us. vet., oral suspension for dogs, Boehringer Ingelheim Vetmedica GmbH, Germany) for one week and famotidine (0.5 mg/kg/bid, p. o., Famotidin Genericon® 20 mg tablets, Genericon Pharma Gesellschaft m.b. H. Graz, Austria) for gastric protection. Due to lack of improvement, one week later meloxicam (0.1 mg/kg/sid, p. o., Metacam® 1.5 mg/ml ad us. vet., oral suspension for dogs, Boehringer Ingelheim Vetmedica GmbH, Germany) was replaced with prednisolone (2 mg/kg/sid, p. o. Prednisolon “Nycomed” 25 mg, Takeda Austria GmbH, Austria) for one week, which was then tapered over one more week.

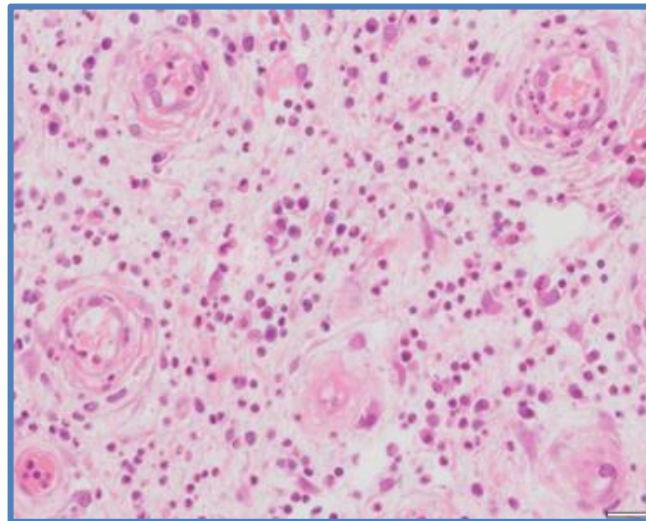


Figure 2 Clearly visible in the histological section are the swollen vessel walls as well as many small vessels that have lost their endothelium. A mixed-cellular inflammatory infiltration is seen with some eosinophils, which are partly present in the vessel wall or directly perivascular.

Unfortunately, this treatment did not achieve a durable clinical remission and a clinical relapse occurred. The owner agreed to a surgical biopsy to remove parts of the affected gingival soft tissue. Histopathology again revealed local eosinophilic stomatitis with extensive ulceration and vasculitis, consistent with earlier findings. Therapy for the relapse included famotidine (0.5 mg/kg/bid, p. o., Famotidin Genericon® 20 mg tablets, Genericon Pharma Gesellschaft m.b. H. Graz, Austria) for five days, amoxicillin and acidum clavulanicum (12.5 mg/kg/bid, p. o., Noroclav Flavour® 50 mg tablets for dogs and cats, Norbrook Laboratories Limited, Ireland and 12.5 mg/kg/bid, p. o., Kesium® 200 mg/50 mg ad us. vet. dividable tablet for dogs,

Biokema SA, Swiss) for seven days, meloxicam (0.1 mg/kg/sid, p. o., Metacam® 1.5 mg/ml ad us. vet., oral suspension for dogs, Boehringer Ingelheim Vetmedica GmbH, Germany) for ten days and famotidine (0.5 mg/kg/bid, p. o., Famotidin Genericon ® 20 mg tablets, Genericon Pharma Gesellschaft m.b. H. Graz, Austria) to prevent gastritis for five days. A switch to hypoallergenic food (Royal Canin® Anallergenic) was implemented for six months. Under therapy the bitch was pain-free. However, the lesions did not disappear with either therapy or the elimination diet.

From May 2015 to October 2016 the patient was examined every three to four months including diagnostic imaging of chest and abdomen to exclude neoplastic diseases as a probable cause of the vasculitis. However, these checks remained unremarkable.

From September 2015 to February 2016 the patient also received treatment with milbemycinoxim and praziquantel (12.5 mg/125 mg per dog, p. o., Milbemax® 12.5 mg/125 mg tablets for dogs, Elanco GmbH, Cuxhaven) once a month to rule out dirofilariasis. During this time faecal examination was performed which was also without abnormalities.

A follow-up biopsy in December 2015, confirmed the eosinophilic inflammation and oedema similar to the previous samples. Between December 2015 and September 2016, several therapeutic attempts were made to induce a clinical remission of the persistent oral lesion. Each new medication started after the previous one failed to show significant improvement. Treatments included ciclosporin (5 mg/kg/sid, p. o., Atopica® 100 mg soft capsules for dogs, Elanco GmbH, Germany) for six weeks, meloxicam (0.1 mg/kg/sid, p. o., Metacam® 1.5 mg/ml ad us. vet., oral suspension for dogs, Boehringer Ingelheim Vetmedica GmbH, Germany) for four weeks, amoxicillin and clavulanic acid (12.5 mg/kg/bid, p. o., Noroclav Flavour® 50 mg tablets for dogs and cats, Norbrook Laboratories Limited, Ireland) for ten days, doxycycline (10 mg/kg/sid, p. o., Vibramycin ® 100 mg solvable tablets Doxycyclin, Pfizer Corporation Austria Ges.m.b.H, Austria) and metronidazole (22 mg/kg/bid) for two weeks, carprofen (4 mg/kg/sid, p. o., Rimadyl® 100 mg ad us. vet. tablets, Zoetis Deutschland GmbH, Germany) for two months, clindamycin (5.5 mg/kg/bid, p.o., Antirobe® 25 mg ad us. vet., capsules for dogs, Zoetis Deutschland GmbH, Germany) for two weeks and prednisolone (2 mg/kg/sid, p. o. Prednisolon "Nycomed" 25 mg, Takeda Austria GmbH, Austria) for seven days, after the dose was tapered to determine the minimum effective dose.

As the eosinophilic vasculitis did not respond to any of the therapies, LDRT in combination with oclacitinib was offered as a rescue treatment option.

On September 15, 2016, another gingival biopsy was taken prior rescue therapy and confirmed the still present eosinophilic vasculitis.

3.3. Irradiation therapy

Radiation was planned and carried out in October 2016. A complete blood count and biochemistry profile was obtained prior anaesthesia and showed a high concentration of eosinophils and slightly increased levels of basophils and monocytes. A planning CT was performed for the computer assisted radiation planning.

The patient was anaesthetised and placed in sternal recumbency on a vacuum cushion. The virtuell isocenter was marked as reference point for the table position. The 3-D-computerasssissted dose calculation was performed with the planning software XIO®, CMS. Two-parallel opposed beams with a field size of 5.6 cm x 10 cm were used for the treatment. A 0.5 cm thick bolus material was placed on the skin surface for dose-build up.



Figure 3 Positioning of the dog for radiation treatment.



Figure 4 Positioning of the dog for radiation treatment.

Four days before the first radiotherapy session the dog was treated with clindamycin (5.5 mg/kg/bid, p. o., Antirobe® 25 mg ad us. vet., capsules for dogs, Zoetis Deutschland GmbH, Germany) for five days and meloxicam (0.1 mg/kg/sid, p. o., Metacam® 1.5 mg/ml ad us. vet., oral suspension for dogs, Boehringer Ingelheim Vetmedica GmbH, Germany) for three days to reduce a secondary bacterial infection which was confirmed in a biopsy prior irradiation.

The patient was irradiated with four daily fractions of 3 Gy and a total dose of 12 Gy. Radiation therapy was delivered with 6MV photons of a linear accelerator (Siemens Primus MidEnergy®,

Siemens Medical Solutions USA Inc, USA) while the patient was under general anaesthesia and in sternal recumbency (Fig. 4, Fig. 5). Additionally, the patient received treatment with prednisolone (0.5 mg/kg/bid, p. o., Prednisolon® 5 mg, tablets for dogs and cats, CP-Pharma Handelsgesellschaft mbH, Germany) using an anti-inflammatory dosage and oclacitinib (0.54 mg/kg/bid, p. o., Apoquel® 5.4 mg ad us. vet, tablets for dogs, Zoetis, Germany) starting on day two of radiotherapy. Prednisolone was reduced three days after the last irradiation to 0.5 mg/kg once daily and stopped three days later. Oclacitinib was given for twelve weeks and was then gradually phased out.

3.4. Follow Up and Outcome

After radiation therapy, a complete clinical remission could be achieved ten days after the end of radiotherapy. The eosinophilic lesions in the oral cavity disappeared and the patient stopped showing signs of pain. As part of a half-yearly dental check-ups, the patient was further carefully examined for any reoccurring eosinophilic lesions. Until the end of the observation period in 2023 the patient remained stable and didn't relapse again. Blood tests carried out at irregular intervals no longer showed an increase in eosinophil granulocytes.

4. Discussion

Cutaneous vasculitis is an immune-mediated inflammatory disease affecting the blood vessels in the skin (1,2). It can be triggered by many factors including infections of bacterial, viral or parasitic origin, insect or tick bites including the transmission of pathogens, food allergies, reactions to drugs or vaccinations, neoplastic diseases and auto-immune diseases (1,4).

Since eosinophilic vasculitis is classified as one of the eosinophilic diseases in dogs, it is worth noting that there is only limited information in the literature as this is a rare group of diseases. In 2019 Mendelsohn et al. reported clinicopathological features, risk factors, and predispositions and treatment response in 24 dogs with eosinophilic oral disease. In this study, medical records from a veterinary teaching hospital and private referral practice were reviewed over a 17-year time-period and 15 breeds, diagnosed with eosinophilic lesions, were presented (22). These lesions were mostly found in the palate and in other oral locations (22). The dogs were managed with different treatment protocols including glucocorticoids, antibiotics (systemic and/or topical), Vitamin E, allergy shots and/or antiparasitic agents as well as exclusion diet or hypoallergenic diet (22). In some cases, an excisional biopsy or laser excision was performed (22). Only 70.8 % of the patients achieved a complete resolution of clinical signs while 25% improved only moderately and 4.2% had little to no improvement (22). 40% of the dogs required long-terms medical management due to continuous clinical signs and persistence of lesions (22).

About 20 years earlier in 1996 a case report was conducted about “Oral eosinophilic granuloma in three Cavalier King Charles spaniels”. All three dogs had one or two ulcerated lesions in the oral cavity (23). Biopsies confirmed the diagnosis of oral eosinophilic lesions and all three dogs were treated with oral prednisolone (2 mg/kg) (23). Only in one of the three dogs the lesions resolved permanently during treatment (23). In one of the other two dogs no remission of the lesions was seen, but the clinical signs such as laboured swallowing and slight reluctance at feeding improved significantly (23). In the third dog the lesions disappeared during treatment but reoccurred shortly after withdrawal of prednisolone and the dog was later euthanized (23).

In cats the feline eosinophilic granuloma complex (EGC) includes various distinct clinical lesions such as indolent or eosinophilic ulcers, eosinophilic plaques and eosinophilic granulomas (24). Possible aetiological triggers include hypersensitivity reactions to flea, food or environmental allergens, infectious diseases of viral, bacterial, fungal or parasitic origin, foreign body reactions, genetic or idiopathic reasons (24). The exact aetiopathogenesis of

EGC remains unclear however evidence points towards an underlying hypersensitivity disorder in affected cats (24). EGC lesions usually show a good response to treatment with systemic glucocorticoids (24). If no response is seen additional therapy with ciclosporin or topical treatment with hydrocortisone aceponate could be considered. Some also suggest the use of systemic chlorambucil or Interferon Omega, as well as prostaglenes (24). In most cases the cats respond well to medical treatment and management, but recurrence is quite common (25).

As mentioned in these papers, there is no explicit treatment strategy for eosinophilic disorders in dogs and cats. Glucocorticoids are usually recommended but the clinical outcome often is unsatisfactory. Often a temporary improvement in both eosinophilic lesions and symptoms are seen but many animals relapse after therapy stopped or need continued medical management. This proves that eosinophilic disorders should not be underestimated and a careful evaluation of the patient's history, diagnostic possibilities and treatment options are essential for the outcome.

Finally in humans the treatment for eosinophil-associated inflammatory disorders includes glucocorticoids and agents against IL-5, IL-5R α and IL-13 (8). IL-5 inhibiting agents mepolizumab and benralizumab are both used for treatment of eosinophilic asthma. Mepolizumab is further indicated to treat eosinophilic granulomatosis and polyangiitis, severe chronic rhinosinusitis and hypereosinophilic syndrome in humans (26). Both drugs are not licensed to be used in veterinary medicine and are further very expensive. The drug dupilumab inhibits IL-4 and IL-13 and is approved for the treatment of atopic dermatitis, asthma, COPD, CRSwNP, Prurigo nodularis and eosinophilic oesophagitis in humans only.

To identify the cause of the eosinophilic vasculitis in this case, different examinations were performed. The patient's history was carefully evaluated and a possible reaction to drugs or vaccinations as well as recent tick bites were ruled out. The owner also explained that the dog did not have any known food allergies. A CBC was performed to exclude an inflammatory process, that possibly could have been triggered by infectious agents. Despite regular deworming a faecal examination was done to check for intestinal parasites and the patient was treated with milbemycin oxim and praziquantel once a month for half a year to exclude a potentially overlooked infection with *Dirofilaria*. The patient also received hypoallergenic food (Royal Canin® Anallergenic) for six months. Neoplastic diseases were ruled out through clinical exams and diagnostic imaging of chest and abdomen. As no abnormalities were detected through these diagnostic work-ups and no underlying cause to trigger the eosinophilic vasculitis could be found, it was described as idiopathic. It is worth mentioning that in order

to identify a cause of the eosinophilic vasculitis, further diagnostic investigations - such as testing for leishmaniosis and antinuclear antibodies - could have been performed. However, these tests were not conducted at that time.

The treatment of idiopathic cutaneous vasculitis in dogs includes immunosuppressants such as glucocorticoids, ciclosporin and azathioprine (4). In difficult cases a combination of these agents is possible (4). Mild cases can be also treated with hemorheological agents such as pentoxifylline and doxycycline (4). In this case the patient was diagnosed with local idiopathic eosinophilic vasculitis and was initially treated with clindamycin and meloxicam. After no visible improvement meloxicam was replaced with prednisolone given at an immune suppressive dosage which was tapered over two weeks. This treatment then led to a temporary improvement, but the dog relapsed shortly after. Treatment with other antibiotics just as doxycycline, metronidazole and clindamycin were also unsuccessful, as well as attempts with the anti-inflammatory agent carprofen. Ciclosporin treatment was initiated but without long lasting improvement and later an immunosuppressive dose of prednisolone was again prescribed for seven days and then the dose was tapered to determine the minimum effective dose. This again could not achieve a durable treatment response and the patient relapsed every time treatment was stopped. Therefore, LDRT in combination with oclacitinib was suggested as a rescue treatment.

LDRT is often used to treat benign diseases and chronic inflammatory conditions such as rheumatism, systemic lupus erythematosus and osteoarthritis in humans (13). However, in small animals LDRT is not used as routine treatment option in non-neoplastic disease yet. LDRT has been reported as a possible treatment method for osteoarthritis and meningoencephalitis of unknown origin in dogs and for osteochondrodysplasia and feline idiopathic cystitis in cats (16,18,19,21,27,28). Many studies including animal models further proved on a cellular level how LDR modulates the immune system (29,30,31,32,33). This includes the different cells, that are involved in the inflammatory response such as endothelial cells, macrophages and lymphocytes but also cytokines.

Endothelial cells play a crucial role in the regulation of local inflammatory processes, both through their ability to recruit blood-derived leukocytes and by their capacity to express a variety of cytokines, chemokines and growth factors (29). The initial contact between leukocytes and endothelial cells is based on the adhesion molecules E- and P-selectin on the endothelial surfaces and to L-selection on the leukocyte surface (34). It has been shown that LDR administered before activation of endothelial cells, resulted in a complete inhibition of E-

selectin expression (34). In human Ea.Hy.926 endothelial cells, LDR prior to stimulation with TNF- α resulted in the induction of Nuclear Factor kappa B (NF- κ B) DNA binding and transcriptional activity (29). Immunologically relevant NF- κ B target genes comprise other molecules like cytokines, TNF- α , adhesion molecules (e.g. E-selectin) and enzymes such as inducible Nitric oxide synthase (iNOS) (29). Additionally, an increased expression and activity of the anti-adhesive cytokine transforming growth-factor-beta 1 (TGF- β 1) was detected in several studies after LDR (13,34,35,36,37).

A pivotal molecular mechanism in the regulation of inflammatory response is the secretion of cytokines (29). These are mediators by which cells of the immune system communicate (30). The profile of cytokine secretion also reflects the functional integrity of the immune system (30). The cytokine TNF- α has a wide range of functions, from the regulation of endothelial cell adhesion molecules to facilitate the entry of leukocytes into tissues to direct induction of cellular cytotoxicity (31). Different studies in OA and EAE mice showed a suppressed TNF- α expression after a 0.5 Gy irradiation, suggesting that a decreased TNF- α production might be involved in the therapeutic effect of LDRT (14,31,32,33). Shin et al. further described a decreased expression of IL-12p70, IFN- γ , IL-13 and IL-17 after chronic low-dose irradiation with 0.2 Gy, indicating suppression of pro-inflammatory responses and allergic inflammation (38). Cytokines IL-12, IL-6 and IL-17 were also decreased in different studies (30,31,32,33,39).

Macrophages constitute the first line of defence against invading pathogens (36). They can promote local inflammation by a variety of functions including phagocytosis, cytotoxicity, antigen presentation, secretion of cytokines, release of reactive oxygen species (ROS) and the expression of iNOS (13,29,34). Activated macrophages express the enzyme iNOS, which through synthesis of nitric oxide (NO) is involved in many physiological and pathophysiological processes such as macrophage-mediated cytotoxicity, vascular permeability, contributes to oedema formation and is also involved in inflammatory pain (29,34,40). After LDR an attenuated expression of iNOS was reported in macrophages (12,35,36,37,40,41). Tsukimoto et al. also found that irradiation with 0.5-1 Gy up-regulates MKP-1 which leads to dephosphorylation of p38MAPK and further results in a suppression of the production of pro-inflammatory cytokines (14). Furthermore, it was shown that irradiation with 0.3-0.6 Gy significantly reduced oxidative burst activity and superoxide production (35,36). Dove et al. also showed that doses of radiation less than 1 Gy can polarize macrophages towards an anti-inflammatory M2 phenotype (12). In contrary to M1 macrophages that activate Th1 cells to

enhance immune response against pathogens or tumour cells, M2 macrophages mediate via type 2 helper cells an anti-inflammatory response (36,42).

Treg cells, which are important in the maintenance of peripheral immune tolerance and in the prevention of immune-mediated diseases by suppressing immune responses, were also found to be significantly increased in irradiated MRL-lpe/lpr mice after irradiation with 0.5 Gy (32,36,43).

Regarding these anti-inflammatory and immunomodulating effects of LDR, this therapy was suggested for the patient in this case report in combination with oclacitinib. This combination therapy then achieved an excellent long-lasting clinical remission without further relapses.

Therefore, LDRT in combination with oclacitinib seems to be a promising rescue option for idiopathic eosinophilic vasculitis in dogs that cannot be controlled by standard therapy alone. Further studies are needed to evaluate if either Oclacitinib or LDRT alone can achieve the same therapeutic effect as the combination therapy. LDRT alone is proven to be a successful treatment in chronic inflammatory and immune-mediated disorders whereas oclacitinib, which is used to treat atopic dermatitis and pruritus associated allergic dermatitis in dogs, has also immunomodulatory, anti-inflammatory and anti-allergic characteristics (5). Further studies evaluated the effect of Oclacitinib on other autoimmune/immune-mediated diseases such as ischaemic dermatopathy, autoimmune subepidermal blistering dermatosis, drug-induced-pemphigus vulgaris, ulcerative ear tip dermatosis, hyperkeratotic erythema multiforme, inherited sensory and autonomic neuropathy, heritable neuropathy, idiopathic rhinitis and canine keratoconjunctivitis sicca (44). These studies all reported a positive outcome of the conditions after treatment with Oclacitinib was initiated. In this case previous treatment with prednisolone alone was not successful in obtaining a long-lasting remission and resulted in a relapse of the oral lesions. However, there are reports that the combination of both, glucocorticoid and radiation therapy, can be more effective than each itself. Marcocci et al. 1991 evaluated the effect of orbital radiotherapy combined with high doses of glucocorticoids for Graves' ophthalmopathy (45). They concluded that the combined treatment is much more effective than radiotherapy or glucocorticoid therapy alone (45). As for oclacitinib, the agent has proven to be an effective adjuvant to a classical treatment with glucocorticoids. Levy et al. evaluated in 2019 the role of oclacitinib in the management of ischaemic dermatopathy in four dogs (46). Juvenile ischaemic dermatopathy is one of several clinically heterogeneous, inflammatory vasculitis presentations in dogs that is often refractory to conventional immunosuppression (46). Of the four dogs that took part in this study a complete remission of

the skin lesions could not be achieved with glucocorticoids alone, nor when these were combined with adjuvant immunosuppressant (46). Oclacitinib treatment was then initiated at the dosage of 0.4-0.7 mg/kg/bid, along with a tapering regimen of prednisolone (46). As a result, a full clinical remission was achieved within four weeks of starting this combination therapy (46). As in this case the patient was treated with LDRT and oclacitinib and we cannot differentiate, if either LDRT or oclacitinib alone can achieve the same long lasting treatment effect as the combination therapy.

Furthermore, there is no standardized LDRT protocol for treating localised lesions of idiopathic eosinophilic vasculitis in dogs. For LDRT usually total doses of 6-12 Gy are used, while the fractionation varies within the literature (9). The patient in this case report was treated with a single dose of 3 Gy per fraction for four days and a total dose of 12 Gy. For comparison Rossi et al. 2018 used a protocol of 3 fractions of 2 Gy for treating OA in dogs, while Kapatkin et al. 2016 used a single dose of 10 Gy to treat elbow OA in dogs (27,47,48). OA is a progressive joint disease associated with degradation of articular cartilage, bone degradation, inflammation of the synovial cells and chondrocyte dysfunction (18,19,27,47). Frequent symptoms are pain and reduced joint range of motion (18,27,47). Different studies evaluated the effect of LDRT on the OA and noticed a significant improvement of lameness and a reduction of pain (19,27,47,48,49). For treating MUO Herzig et al. 2023 considered a protocol of five daily fractions of 4 Gy effective (28). MUO is believed to be the result of an aberrant immune response against the antigens located in CNS, but the exact pathomechanism is still not completely understood (28). Herzig et al. 2023 treated 10 dogs diagnosed with MUO with a shortened whole brain irradiation of 5 x 4 Gy in combination with prednisolone (28). The neurological status in all dogs improved during radiation therapy (28). In two dogs the MRI lesions resolved completely while they partially resolved in five out of ten dogs (28). Idiopathic cystitis is a painful inflammatory bladder condition that brings about extreme discomfort, frequent urination and in some cases inappropriate elimination in the home (50). Cats treated with LDR experienced significant relief from these symptoms (51). The radiation thereby targets the root causes of the idiopathic cystitis, reducing bladder inflammation, alleviating pain and improving quality of life for affected cats (50). As a protocol the State NC State College of Veterinary Medicine used a single fraction of 6 Gy to treat the idiopathic cystitis in cats (52). At the American College of Veterinary Radiology Congress Gieger et al. 2023 presented their studies about the radiation treatment of cats suffering from enteropathy-associated T cell lymphoma or inflammatory bowel disease (20). They chose a radiation protocol of 4 x 2 Gy

and noticed a significant clinical improvement in most cats (20). Except for one protocol all authors used the recommended total dose of 6 -12 Gy. And most important, all studies found their protocols to be effective in the treatment of the evaluated inflammatory diseases.

In conclusion, the combination therapy of LDRT and oclacitinib resulted in a fast and long-lasting treatment response in a dog suffering from relapsing idiopathic eosinophilic vasculitis. These promising results in a single case have to be confirmed in larger patient numbers. Further, future studies need to investigate if either LDRT or oclacitinib alone can achieve the same effect as the combination therapy.

5. Conclusion

Low-dose radiation therapy represents a possible treatment approach for chronic inflammatory and immune-mediated disorders in small animals. In this case report, a dog suffering from localised oral idiopathic eosinophilic vasculitis, was treated with low-dose radiation therapy in combination with oclacitinib. Before different treatment approaches such as glucocorticoids, ciclosporin, doxycycline, antibiotics and NSAIDs were tried, but the dog only responded temporarily and no long-term improvement was seen. The patient was then treated with low-dose radiation with a total dose of 12 Gy in combination with Oclacitinib. This combination therapy achieved an excellent long-lasting clinical remission without further relapses. To the best of our knowledge, this case report describes for the first time the successful treatment of a refractory idiopathic eosinophilic vasculitis with low-dose radiation therapy and oclacitinib. Future studies are needed to confirm our findings and investigate if either low-dose radiation therapy or oclacitinib alone can achieve the same long lasting treatment effect as the combination therapy.

6. References

- 1 Innerå M. Cutaneous Vasculitis in Small Animals. *Vet Clin Small Anim* 2013; 43: 113- 134
- 2 Morris DO, Beale KM. Cutaneus vasculitis and vasculopathy. *Veterinary Clinics of North America: Small Animal Practice* 1999; 29 (6): 1325-1335
- 3 Kohn B, Schwarz G. *Praktikum der Hundeklinik*. 12th Ed., aktualisierte Auflage. Stuttgart: Enke Verlag; 2017 doi:10.1055/b-004-140269
- 4 Miller WH, Griffin CE, Campbell KL. *Muller & Kirk's Small Animal Dermatology*. 7th Ed. St. Louis: Elsevier Mosby; 2013
- 5 Institute of Pharmacology and Toxicology Vetsuisse Faculty. Wirkstoff Oclacitinib. https://www.vetpharm.uzh.ch/Wirkstoffe/000000120831/9269_04.html (27.11.2024)
- 6 Paneez K, Grayson PC, Klion AD. Eosinophils in vasculitis: characteristics and roles in pathogenesis. *Nature Reviews Rheumatology* 2014; 10(8): 474-483
- 7 Vega Villanueva KL, Espinoza LR. Eosinophilic Vasculitis. *Current Rheumatology Reports* 2020; 22(5)
- 8 Gigon L, Fettlelet T, Yousefi S, Simon D, Simon H-W. Eosinophils from A to Z. *Allergy* 2023; 78:1810-1846
- 9 Wechsler et al. Eosinophils in Health and Disease. A State-of-the-Art Review. *Mayo Clinic Proceedings* 2021; 96(10): 2694-2707
- 10 Kleiter M. *Strahlentherapie an der Vetmeduni Vienna – Wissenswertes für den zuweisenden Tierarzt*. Tierärzte Verlag 2018
- 11 Torres Royo L, Antelo Redondo G, Árcuez Pianetta M, Arenas Prat M. Low-Dose radiation therapy for benign pathologies. *Reports of Practical Oncology and Radiotherapy* 2020; 25: 250–254
- 12 Dove APH, Cmelak A, Darrow K, McComas KN, Chowdhary M, Beckta J, Kirschner AN. The Use of Low-Dose Radiation Therapy in Osteoarthritis: A Review. *International Journal of Radiation Oncology Biology Physics* 2022; 114: 203-220
- 13 DEGRO-AG "Radiotherapy of Benign Diseases". Guidelines in Radiotherapy. Radiotherapy for benign diseases. Specialist group-specific evidence-based S2e

guideline of the German Society for Radiation Oncology (DEGRO). Version 3.0. from 2022

- 14 Tsukimoto M, Homma T, Mutou Y, Kojima S. 0.5 Gy Gamma Radiation Suppresses Production of TNF- α through Up-regulation of MKP-1 in Mouse Macrophage RAW264.7 Cells. *Radiation Research* 2009; 171: 219-224
- 15 Kojima S, Tsukimoto M, Shimura N, Koga H, Murata A, Takara T. Treatment of Cancer and Inflammation With Low-Dose Ionizing Radiation: Three Case Reports. *Dose Response: An International Journal* 2017; 1-7
- 16 Penelas A. Strahlentherapie zur Schmerzbehandlung degenerativer Gelenkerkrankungen beim Hund: Subjektive und objektive Evaluation der Wirksamkeit (Dissertation). Vetsuisse Fakultät Universität Zürich; 2015
- 17 Pommer A. Röntgentherapie der Hautkrankheiten bei Hunden und Katzen. Sonderabdruck aus der Wiener Tierärztlichen Monatsschrift XXI. 1934; 10, 14, 18 & 24
- 18 Eberle N. Einsatz der Strahlentherapie zur Schmerzbehandlung bei Hund und Katze. *Der Praktische Tierarzt* 2018; 99: 24-32
- 19 Voss A-Ch, Heuschmann I. Röntgenreizbestrahlungen bei 60 Hunden mit Osteoarthrosen. *Tierärztli Prax* 2008; 36: 339-345
- 20 Gieger T, Nolan M, Gookin J, Watson VE. Use of Radiation Therapy (2 Gy x 4) to Treat Feline Chronic Enteropathies. *American College of Veterinary Oncology Congress* 2023
- 21 Kendall A, Nolan M, Enders B, Vaden S. Abstract NU12: Low-dose radiation therapy: a novel treatment for feline idiopathic/interstitial cystitis. 2023 ACVIM Forum research abstract program. *Journal of Internal Veterinary Medicine* 38, 713–4, 2024
- 22 Mendelsohn D, Lewis JR, Iglesias Scott K, Brown DC, Reiter AM. Clinicopathological Features, Risk Factors and Predispositions, and Response to Treatment of Eosinophilic Oral Disease in 24 Dogs (2000-2016). *Journal of Veterinary Dentistry* 2019; 36(1): 25-31
- 23 Bredal WP, Gunnes G, Vollset I, Ulstein TL. Oral eosinophilic granuloma in three Cavalier King Charles spaniels. *Journal of Small Animal Practice* 1996; 37: 499-504
- 24 Buckley L, Nuttall T. Feline Eosinophilic Granuloma Complex(ities): Some clinical clarification. *Journal of Feline Medicine and Surgery* 2012; 14: 471-481

- 25 Weir M, Hunter T, Ward E. Eosinophilic Granuloma Complex in Cats. <https://vcahospitals.com/know-your-pet/feline-eosinophilic-granuloma-complex-in-cats#> (27.10.2024)
- 26 <https://www.ema.europa.eu/en/medicines/human/EPAR/nucala> (27.11.2024)
- 27 Rossi F, Cancedda S, Leone VF, Rohrer Bley C, Laganga P. Megavoltage Radiotherapy for the Treatment of Degenerative Joint Disease in Dogs: Results of a Preliminary Experience in an Italian Radiotherapy Centre. *Frontiers in Veterinary Science* 2018; 5
- 28 Herzig R, Beckmann K, Körner M, Steffen F, Rohrer Bley C. A shortened whole brain radiation therapy protocol for meningoencephalitis of unknown origin in dogs. *Frontiers in Veterinary Science* 2023; 10:1132736.
- 29 Rödel F, Frey B, Gaipl U, Keilholz L, Fournier C, Manda K, Schöllnberger H, Hildebrandt G, Rödel C. Modulation of Inflammatory Immune Reactions by Low-Dose Ionizing Radiation: Molecular Mechanisms and Clinical Application. *Current Medicinal Chemistry* 2012; 19: 1741-1750
- 30 Bogdándi EN, Balogh A, Felgyinszki N, Szatmári T, Persa E, Hildebrandt G, Sáfrány G, Lumniczky K. Effects of Low-Dose Radiation on the Immune System of Mice after Total-Body irradiation. *Radiation Research* 2010; 174: 480-489
- 31 Tsukimoto M, Nakatsukasa H, Sugawara K, Yamashita K, Kojima S. Repeated 0.5-Gy γ Irradiation Attenuates Experimental Autoimmune Encephalomyelitis with Up-regulation of Regulatory T Cells and Suppression of IL17 Production. *Radiation Research* 2008; 170(4): 429-436
- 32 Nakatsukasa H, Tsukimoto M, Tokunaga A, Kojima S. Repeated Gamma Irradiation Attenuates Collagen-Induced Arthritis via Upregulation of Regulatory T Cells but not by Damaging Lymphocytes Directly. *Radiation Research* 2010; 174(3): 313-324
- 33 Nakatsukasa H, Tsukimoto M, Ohshima Y, Tago F, Masada A, Kojima S. Suppressing effect of low-dose gamma-ray irradiation on collagen-induced arthritis. *Radiation Research* 2008; 49: 381-389
- 34 Rödel F, Keilholz L, Herrmann M, Sauer R, Hildebrandt G. Radiobiological mechanisms in inflammatory diseases of low-dose radiation therapy. *International Journal of Radiation Biology* 2007; 83: 357 – 366

- 35 Lumniczky K, Impens N, Armengol G, Candéias, Georgakilas AG, Hornhardt, Martin OA, Rödel F, Schaue D. Low dose ionizing radiation effects on the immune system. *Environ Int.* 2021; 149: 106212
- 36 Frey B, Hehlhans S, Rödel F, Gaipf US. Modulation of inflammation by low and high doses of ionizing radiation: Implications of benign and malignant diseases. *Cancer Letters* 2015; 368: 230-237
- 37 Schaue D, Jahns J, Hildebrandt G, Trott KR. Radiation treatment of acute inflammation in mice. *International Journal of Radiation Biology* 2005; 81(9): 657-667
- 38 Shin SC, Lee K-M, Kang YM, Kim K, Kim C, Yang KH, Jin Y-W, Kim CS, Kim HS. Alteration of cytokine profiles in mice exposed to chronic low-dose ionizing radiation. *Biochemical and Biophysical Research Communications* 2010; 397: 644-649
- 39 Tanaka T, Tago F, Fang S, Shimura N, Kojima S. Repeated 0.5-Gy γ -ray irradiation attenuates autoimmune manifestations in MRL-lpr/lpr mice. *International Journal of Radiation Biology* 2005; 81: 731-740
- 40 Hildebrandt G, Seed MP, Freemantle CN, Alam CAS, Colville-Nash PR, Trott KR. Mechanisms of the anti-inflammatory activity of low-dose radiation therapy. *International Journal of Radiation Biology* 1998; 74(3): 367-378
- 41 Calabrese EJ, Calabrese V. Low dose radiation therapy (LD-RT) is effective in the treatment of arthritis: Animal model findings. *International Journal of Radiation Biology* 2013; 89(4): 287-294
- 42 Song H-Y, Chen F, Park HR, Han JM, Ji HJ, Byun E-B, Kwon Y, Kim M-K, Ahn KB, Seo HS. Low-dose radiation therapy suppresses viral pneumonia by enhancing broad-spectrum anti-inflammatory responses via transforming growth factor- β production. *Frontiers in Immunology* 2023
- 43 Tago F, Tsukimoto M, Nakatsukasa H, Kojima S. Repeated 0.5-Gy Gamma Irradiation Attenuates Autoimmune Disease in MRL-lpr/lpr Mice with Suppression of CD3+CD4-CD8-B220+ T-Cell Proliferation and with Up-regulation of CD4+CD25+Foxp3+ Regulatory T Cells. *Radiation Research* 2008; 169(1): 59-66
- 44 Marsella R, Doerr K, Gonzales A, Rosekrantz W, Schissler J, White A. Oclacitinib 10 years later: lessons learned and directions for the future. *Journal of the American Veterinary Medical Association.* 2023; 261

- 45 Marcocci C, Baralens L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A: Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves 'ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. *Journal of Endocrinological Investigation* 1991; 14: 853-860
- 46 Levy BJ, Linder KE, Olivry T. The role of oclacitinib in the management of ischaemic dermatopathy in four dogs. *Veterinary Dermatology* 2019
- 47 Solis DB, Mayer MN. Low dose radiation therapy for the treatment of refractory canine osteoarthritis. *Canadian Veterinary Journal* 2022; 63
- 48 Kapatkin AS, Nordquist B, Garcia TC, Griffin MA, Theon A, Kim S, Hayashi K. Effect of a single dose radiation therapy on weight-bearing lameness in dogs with elbow osteoarthritis. *Vet Comp Orthop Traumatol* 2016; 29: 338–343
- 49 Welsch B. Strahlen gegen Arthrosen. *Gesellschaft zur Förderung Kynologischer Forschung – Neue gkf-Projekte* 2014; Info 40
- 50 PetCure Oncology. Hope for cats with chronic bladder issues: low-dose radiation treatment for feline cystitis. <https://petcureoncology.com/cats-chronic-bladder-issues-radiation-treatment-feline-cystitis/> (28.02.2025)
- 51 PetCure Oncology. Low-dose radiation treatment for benign (non-cancerous) chronic conditions. <https://petcureoncology.com/low-dose-radiation-treatment-non-cancerous-conditions/> (20.02.2025)
- 52 Wheeler BE. Study's Cystitis Remedy so Effective that NC State Ready to Offer Treatment to Cats. *Veterinary Medicine News* 2023. <https://news.cvm.ncsu.edu/studys-cystitis-remedy-so-effective-that-nc-state-ready-to-offer-treatment-to-cats/> (20.02.2025)

7. List of figures

- Figure 1 Figure 1 Eosinophilic plaques in the oral cavity, 1a before treatment with antibiotics, 1b after treatment with antibiotics. Eberspächer-Schweda 2015
- Figure 2 Clearly visible in the histological section are the swollen vessel walls as well as many small vessels that have lost their endothelium. A mixed-cellular inflammatory infiltration is seen with some eosinophils, which are partly present in the vessel wall or directly perivascular. Richter B. 2015
- Figure 3 Positioning of the dog for radiation treatment. Kleiter M. 2016
- Figure 4 Positioning of the dog for radiation treatment. Kleiter M. 2016

