Treatment of Calcinosis Cutis with Minocycline in Five Dogs

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Abstract: Calcinosis cutis is a chronic condition characterized by insoluble calcified deposits in the skin and subcutaneous tissue. Although there is no uniformly effective treatment for calcinosis cutis, minocycline therapy has demonstrated varying degrees of benefit in humans. Five client-owned dogs with calcinosis cutis were included. Minocycline was administered orally in a dose of 10 mg/kg bodyweight twice a day. Treatment was repeated every day until complete remission. The efficacy of minocycline was evaluated within this period. The side effects of minocycline were monitored and reported by the owners and veterinarians. Of the 5 dogs with calcinosis cutis, which was classified as the dystrophic form, four dogs had a complete remission of calcinosis cutis and one dog had a partial response. The major improvement was a reduction in the size of the calcified deposits and reduction in inflammation associated with them. The duration of remission was 9.1 ± 2.2 weeks. The adverse effects, observed in one dog, were anorexia and vomiting. Minocycline may be effective in the control of calcinosis cutis in dogs.

Key words: dog, calcinosis cutis, minocycline, treatment.

Introduction

Calciosis cutis is an uncommon canine skin disorder, in which inorganic, insoluble mineral salts, such as calcium phosphate and hydroxyapatite are deposited in the dermis, epidermis, or subcutis (5,7,10). The pathological process of calcification in soft tissues is highly complex and not fully understood, but changes in collagen and elastic fibers may induce phase transformation from ions such as calcium and phosphate to the solid phase (7,11,21). Calciosis cutis can be secondary to, or associated with a number of disorders (5). Calciosis cutis has been broadly classified into four categories: dystrophic, metastatic, idiopathic, and iatrogenic (5,8,12).

Dystrophic calciosis cutis is the most common form in dogs; it usually occurs as a result of hyperadrenocorticism and local tissue injury, but has also been reported in association with systemic diseases such as diabetes mellitus, systemic fungal infections or leptospirosis (5,8,11). Metastatic calciosis cutis, which is mostly associated with chronic renal disease, is rarely seen in dogs (11). Metastatic calcification occurs when serum calcium and/or phosphorus concentration is elevated, resulting in a serum calcium × phosphorus product > 70 mg/dL or > 5.6 mmol/L, which predisposes to calcium deposition within the tissue (7,8). In idiopathic calciosis cutis, there is no clear underlying tissue damage or metabolic disorder (8). It has rarely been observed in healthy dogs younger than 1 year and also after systemic illness in puppies (8,11). Iatrogenic calciosis cutis has been reported after percutaneous absorption of a calcium-containing landscaping product or subcutaneous injection of calcium-containing solutions administered for hypoparathyroidism treatment (8,11).

Minocycline is a broad-spectrum bacteriostatic antibiotic related to the tetracycline family (1,17). It is more lipophilic, absorbable and long-acting than tetracycline (14). Minocycline has other actions and effects in addition to its antibacterial properties (14,17,19). It chelates calcium and iron, influences osteoclast function, inhibits inflammation, angiogenesis, and function of matrix metalloproteinases (MMPs) (17,19). The most common adverse effects are nausea and vomiting (16).

In humans, various treatments for calciosis cutis have been reported as successful, including minocycline, warfarin, probenecid, colchicine, diltiazem, and intralesional corticosteroids (15). However, there is no standardized therapy in dogs. One study reported that treatment with dimethyl sulfoxide (DMSO) gel may accelerate resolution of the lesions (2). The aim of this study was to evaluate the effect and safety of minocycline as treatment for calciosis cutis in dogs.

Case

Five client-owned dogs with calciosis cutis were included, obtained from the Chungnam National University Veterinary Medical Teaching Hospital. Diagnosis of calciosis cutis and its subtypes was based on history, physical examinations, radiological, laboratory, cytological and histopathological examinations. In physical examinations, affected sites and gross lesions were investigated. To determine infiltration of calcium into the subcutis, X-ray was performed. Laboratory examinations were performed to determine the subtype of calciosis. The following tests were performed: complete blood count, serum chemistry, electrolytes assay and hormone assay with ACTH stimulation. Punch biopsy was performed for histopathological examination.
Minocycline (Minocin; Daewoong Pharmaceutical, Korea) was administered orally at a dose of 10 mg/kg bodyweight twice a day. Treatment was repeated every day until complete remission. Primary or secondary disorders of calcinosis cutis were also treated appropriately.

The efficacy of minocycline was evaluated within the

<table>
<thead>
<tr>
<th>Patient</th>
<th>Breed</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Affected area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shih-Tzu</td>
<td>18</td>
<td>MC</td>
<td>6.5</td>
<td>Head, tail</td>
</tr>
<tr>
<td>2</td>
<td>Shih-Tzu</td>
<td>10</td>
<td>M</td>
<td>7.2</td>
<td>Head, dorsum, inguinal</td>
</tr>
<tr>
<td>3</td>
<td>Shih-Tzu</td>
<td>9</td>
<td>MC</td>
<td>6.5</td>
<td>Tongue, dorsum, thorax</td>
</tr>
<tr>
<td>4</td>
<td>Miniature Schnauzer</td>
<td>11</td>
<td>FS</td>
<td>7.3</td>
<td>Axilla, inguinal</td>
</tr>
<tr>
<td>5</td>
<td>Pekingese</td>
<td>7</td>
<td>F</td>
<td>6.8</td>
<td>Dorsum, lumbar</td>
</tr>
</tbody>
</table>

F, female; FS, female spayed; M, male; MC, male castrated.

**Fig 1.** Lateral images demonstrating calcinosis cutis in the subcutis of the dorsal thorax (left) and the lumbar area (right) on radiographic examinations.

**Fig 2.** Diffuse basophilic stained mineral deposits extending from the superficial to mid dermis. Hematoxylin and eosin, × 100 (left), Von Kossa stain, × 100 (right).

**Fig 3.** Before treatment, erythematous, popular plaques were on the head (left). After 7 weeks of minocycline treatment, a complete remission of alopecia and redness was observed (right).
period in which the lesions were completely cured. The appearance of calcinosis cutis was assessed clinically at routine follow-up examinations. Side effects of minocycline were monitored and reported by the owners and veterinarians.

The breed distribution in this study was as follows: Shih-Tzu was represented by three of the five dogs, whereas the other two dogs were Miniature Schnauzer and Pekingese. Their ages at the time of diagnosis ranged from 7 to 18 years (average 11.0 ± 4.2 years). Three dogs were male and two dogs were female. The mean body weight was 6.9 ± 0.4 kg (range, 6.5-7.3 kg) (Table 1). According to dermatological tests, all dogs had firm, palpable nodules and well-demarcated masses in multiple regions of the body. Lesions were found in the dorsum, ventral thorax, axilla, inguinal region, groin, head, and tongue. Crusts, epidermal collarettes, scales, fissures, erythema and alopecia were also evaluated as secondary dermatologic lesions with pruritus and pain.

On radiologic examinations, radiopaque substances were observed in subcutaneous of the lesions (Fig 1). Histopathology showed diffuse mineral deposition stained basophilic in hematoxylin and eosin, which extended into the dermis. The Von Kossa stain, revealed diffuse dark brown to black mineral deposit in the dermis (Fig 2).

In all dogs treated in this study, calcinosis cutis was classified as the dystrophic form. The underlying disorders were iatrogenic hyperadrenocorticism (4 dogs) and spontaneous hyperadrenocorticism (1 dog). Diseases treated with prednisolone that resulted in iatrogenic hyperadrenocorticism were atopic dermatitis (4 of 5). The duration of corticosteroid therapy before the onset of calcinosis cutis was 14 weeks.

In one dog, the concentration of serum calcium was 10.0 mg/dL (reference range; 8.5-12.0 mg/dL) and serum phosphorus was 7.4 mg/dL (reference range; 2.5-5.5 mg/dL). Thus serum calcium x phosphorus amounted to 74.0 mg/dL. The dog had normal levels of BUN and creatinine and showed no structural changes in the kidney, as revealed by ultrasonography. All other dogs had normal serum calcium and phosphorus levels.

Complete remission of calcinosis cutis after minocycline treatment (no dermatologic lesions or relapse) occurred in 4 dogs (Fig 3). The mean duration of treatment of these patients was 9.1 ± 2.2 weeks (range, 6-12 weeks). One dog with partial improvement had discontinuous therapy.

Although minocycline was ingested with food, one dog had side effects. One dog had anorexia, therefore, the drug dosage was reduced to 7 mg/kg, following this reduction, no more adverse effects were observed during the treatment.

**Discussion**

All dogs in this study responded to minocycline and 4 dogs had a complete remission of calcinosis cutis. The duration of treatment in these dogs was 9.2 ± 1.9 (range, 7-12) weeks. One dog had a partial response during 12 weeks of therapy. Dogs experienced a decrease in the size of calcinosis deposits and healing of associated skin lesions. The duration of treatment in the study was reduced in comparison with previous reports. In dogs with dystrophic calcinosis cutis and hyperadrenocorticism, correcting the underlying causes resulted in regression of calcinosis within 2 to 12 months without additional therapy (11). In another report, four dogs with iatrogenic hyperadrenocorticism had calcinosis cutis permanently until the underlying causes were corrected (9).

The precise mechanisms by which minocycline affects calcinosis cutis are not completely understood (17). Four major mechanisms of minocycline action have been suggested, as described below.

Minocycline inhibits MMPs. This function is the most widely documented and best characterized non-antibiotic property of tetracyclines (14). The MMPs are zinc-dependent proteases produced by inflammatory cells and resident connective tissue cells (14). They have the ability to break down structural proteins of the extracellular matrix and thereby play an important role in inflammation, wound healing, embryogenesis, or tumor invasion and metastasis (14). Normally, proteolytic activity of MMPs is regulated by their precursors and by endogenous inhibitors, α-macroglobulins, and tissue inhibitors of MMPs (13). When MMPs are present in a lesion at a high level, for a long a time, and at non-physiological locations, they degrade proteins and this causes problems (13). The 30 identified MMPs belong to three major classes: collagenases, gelatinases and stromelysins (14). Minocycline and related compounds inhibit both collagenases (MMP-1, MMP-8 and MMP-13) and gelatinases (MMP-2 and MMP-9), which have important roles in inflammation and wound healing (14,18,19). Inhibition of MMPs is thought to reduce inflammation and collagen damage in calcinosis cutis.

Minocycline also has anti-inflammatory properties. It inhibits leukocyte migration, and suppresses T cell proliferation and reduces the production of interleukin-2, interferon-γ and tumor necrosis factor-α (14).

Minocycline and related compounds are broad-spectrum antibiotics, which bind to the 30S ribosomal subunit and inhibit bacterial protein synthesis (8). Thus, they may help treat secondary infections associated with calcinosis cutis.

Minocycline and other tetracyclines are well known chelators of divalent metal cations (14,19). They circulate as calcium ion chophones (19). Tetracycline was found to be a potent anticalcification agent in an ectopic calcification model (4). It is possible that minocycline reduces the level of calcium in the lesions.

Minocycline treatment was well tolerated, with only one dog having gastrointestinal side effects. These side effects appear to be dose-dependent, as side effects were eliminated reducing the dose of minocycline from 10 mg/kg to 7 mg/kg. The most commonly reported side effects of oral minocycline therapy in dogs are nausea and vomiting (14). Minocycline is more lipophilic than tetracycline and thus, has much less gastrointestinal side effects (14,17).

Few treatment options for canine calcinosis cutis have been reported. Adjunctive topical treatment with DMSO gel every 24 h may help resolve the lesions (17). We used diltiazem in another case of calcinosis cutis, and the dog had a complete remission within 17 weeks of treatment (3).

The lesions observed in this study varied. The distribution of the affected areas was not an indication of a particular underlying disease. The most affected region was the dor-
calcinosis cutis lesions among 28 dogs with iatrogenic hyperadrenocorticism, ranging from 1.7% to 40% (8). There is a report that only 4 dogs had calcinosis cutis in dogs with hyperadrenocorticism, ranging from 1.7% to 40% (8). There is a report that only 4 dogs had calcinosis cutis lesions among 28 dogs with iatrogenic hyperadrenocorticism. There has been significant variability in the reported prevalence of calcinosis cutis lesions among 28 dogs with iatrogenic hyperadrenocorticism (14.3%) (20).

Minocycline is effective in the control of calcinosis cutis in dogs. There are probably multiple mechanisms of action of this drug, but we suggest four major mechanisms to explain its effect on calcinosis cutis, especially MMPs inhibition, which might be the predominant mechanism. The drug appears to be generally well tolerated. To determine the efficacy of minocycline for calcinosis cutis treatment, dogs with various forms of calcinosis cutis should be included in view of the substantial benefits seen in this study.

Acknowledgements

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References