

## Minocycline as a treatment of dog with calcinosis cutis

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**Abstract :** An 8-year-old, castrated male, Schnauzer dog was presented for evaluation of gradually worsening erythematous papules. Physical examination revealed multiple erythematous papules having a firm, gritty texture located in bilateral ears, dorsal midline, perianal and inguinal area. Skin biopsy revealed aberrant structure, characterized by atrophic epidermal-dermal layer structure with granular materials which was presumed as calcinosis cutis secondary to iatrogenic hyperadrenocorticism. By initiating minocycline for 14 days, there was reduction in size, number of calcium deposit with remarkably decreased erythema. This case report presents the clinical trial of minocycline as a potential agent in treating dogs with calcinosis cutis.

**Keywords :** calcinosis cutis, dog, iatrogenic hyperadrenocorticism, minocycline

Calcinosis cutis is a term to describe abnormal calcium deposits forming in the dermis, epidermis, or subcutis [2, 3]. Calcification of the skin may occur in a wide variety of disorders. It is most commonly developed as a result of naturally occurring or iatrogenic hyperadrenocorticism (HAC) in dogs [4, 12]. The mechanisms of calcification are divided into four categories: dystrophic, metastatic, iatrogenic and idiopathic [4]. Dystrophic calcification is the most common type and it is associated with local tissue damage or disorders in collagenous, elastic, or subcutaneous tissue [8]. Metastatic calcification is related to the accumulation of calcium salts in normal tissue, associated with aberrant metabolism of calcium and phosphorus [6]. Iatrogenic calcification appears secondary to penetration of calcium containing products and idiopathic calcification is in the absence of identifiable local or systemic factors such as local tissue damage or metabolic disorders [4]. As dystrophic calcification commonly occurs in association with canine HAC that leads to calcinosis cutis [1], diagnoses on hematologic and biochemical profile present hypercortisolism with normal calcium and phosphorus levels typically found [4, 5].

Cutaneous lesions consist of erythematous papule, plaques, and nodules frequently ulcerated and secondarily infected. The lesions often affect especially along the dorsum, axillae and the inguinal region [12]. Radiographs reveal calcified mass in skin and by performing skin biopsy, multifocal deposits of granular materials can be observed in dermal, subcutaneous tissue [3, 8].

As calcinosis cutis is a rare disorder, no standard therapy

has been generally accepted. However, several treatments have been reported beneficial in human medicine, including warfarin, bisphosphonates, probenecid, ceftriaxone, diltiazem and minocycline [9].

This case describes beneficial effects of skin lesions in iatrogenic HAC following minocycline treatment.

An 8-year-old, castrated male, Schnauzer dog was initially presented for evaluation of numerous erythematous papules which appeared 6 weeks ago and gradually increased in number and size. The dog had a history of long term orally administered corticosteroids for 8 years continuously to treat allergic dermatitis. On physical examination, the skin was thin on palpation and there were lesions consisting of multiple erythematous, crusted papules located in the dermis of both sides of the ears, dorsal midline, perianal and inguinal area, having a firm, gritty texture (Figs. 1A-C). Also hepatomegaly was present on abdominal palpation. A complete blood count showed thrombocytosis ( $666 \times 10^3/\mu\text{L}$ ; reference range:  $200\sim 500 \times 10^3/\mu\text{L}$ ) with mild stress leukogram and serum chemistry profile revealed marked elevation in alanine aminotransferase (278 U/L; reference range: 19~70 U/L), alkaline phosphatase (3817 U/L; reference range: 15~127 U/L), gamma-glutamyl transpeptidase (118 mg/dL; reference range: 0~6 mg/dL) with increased triglycerides (302 mg/dL; reference range: 19~133 mg/dL) and hypercalcemia (12.2 mg/dL; reference range: 8.8~11 mg/dL) (Table 1).

Dermatological examinations for the skin lesions were conducted. Skin taping, scraping, trichogram and wood's lamp tests were unremarkable. Bacterial and fungal cultures

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**Fig. 1.** Photographs of progress of calcinosis cutis lesion in bilateral ears, dorsal midline and perianal region. Appearance of multiple calcium deposit lesions with marked erythema and alopecia which is predisposed to secondary infection (A-C). Fourteen days after treatment with minocycline. Remarkable reduction of size and number of papules were noted and erythematous cutaneous lesions disappeared (D-F).

**Table 1.** Profiles of relevant serum biochemical findings

Parameters	Day 1	Day 2	Day 30	Reference range
Alanine aminotransferase (U/L)	278	250	139	19~70
Alkaline phosphatase (U/L)	3817	3766	2617	15~127
Gamma-glutamyl transpeptidase (U/L)	118	102.4	28.1	0~6
Triglyceride (mg/dL)	302	160	399	19~133
Calcium (mg/dL)	12.2	11.1	10	8.8~11
Ionized Calcium (mmol/L)	1.38	1.33	–	1.1~1.3
Inorganic phosphorus (mg/dL)	2.9	3.3	2.4	3.0~6.2

were all negative. Representative skin biopsy samples were taken from skin in the inguinal area and were evaluated to discover the underlying cause. Histopathologically, thin epidermal-dermal layer characterized by atrophic hair follicles, adnexal glands and multifocal accumulations of coarsely granular amorphous basophilic materials were identified in deep dermal tissue (Figs. 2A and B).

Radiography revealed hepatomegaly and displacement of stomach caudally and dorsally. Multiple rounded, dense, amorphous calcified materials were detected on the dorsal subcutis. On ultrasonography, hyperechoic foci smaller than 1mm were scattered in soft tissues including the spleen and bilateral renal cortex.

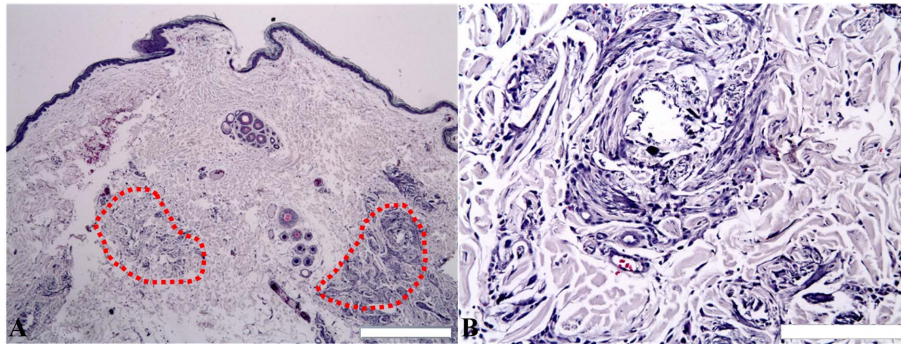
Echocardiography was performed because the dog had hypertension (151 mmHg, Cardell model 9401; Dan Scott & Associates, USA) and slight cardiomegaly (Vertebral Heart Score, VHS = 10.8, normal range;  $9.7 \pm 0.5$ ) and revealed

thickened cardiac wall with hyperechoic spots of cardiac muscle.

Based on the results described previously, the association of calcinosis cutis with iatrogenic HAC was considered, additional tests including serum parathyroid hormone (PTH) level and adrenocorticotropic hormone (ACTH) stimulation test were performed for confirmation, revealing normal PTH level with normal pre (1.47  $\mu\text{g/dL}$ ; reference range: 1.0~6.0  $\mu\text{g/dL}$ ) and low post (1.75  $\mu\text{g/dL}$ ; reference range: 5.50~20.00  $\mu\text{g/dL}$ ) cortisol level.

Based on history, laboratory tests and dermatologic examinations including histopathologic findings, dystrophic calcinosis cutis following iatrogenic HAC was diagnosed and corticosteroid treatment was discontinued for a month.

At 4 week follow-up, the serum biochemical findings revealed lowered levels of hepatobiliary enzymes including ALT, ALP, GGT. However, there was no improvement in



**Fig. 2.** Histopathologic appearance of the biopsy in inguinal region. (A) Atrophy of epidermis and skin adnexa with marked deposition of calcium at the sites of crystal formation and along degenerating collagen fibers (dotted line). (B) The region of calcification is observed as dark purple. H&E stain, Scale bars = 500  $\mu$ m (A), 100  $\mu$ m (B).

skin lesions. Thus, we initiated prescription of minocycline (15 mg/kg, PO, q12hr, Minocin; SK chemical, Korea) for 2 weeks and noticed both reduction in size, number of papules and alleviation of erythema with no spreading of calcium deposits to other areas (Figs. 1D-F). After 4 week of treatment with minocycline, skin lesions were resolved and no other adverse reaction was noticed.

Calcinosis cutis is characterized by inappropriate deposition of insoluble calcium within the skin. It is the specific type of dystrophic calcium deposits and occurs most commonly secondary to iatrogenic HAC [2, 3]. It is probably caused by protein catabolic functions of cortisol which results in damage to the structure within collagen and elastin, predisposing calcium precipitation in the skin [4]. In addition, local tissue damage and necrosis increases cell membrane permeability, allowing cytosolic influx of sufficient calcium that exceeds the capacity of mitochondria. As a result, abnormally high mitochondrial calcium and phosphate may lead to crystal deposition and cell necrosis which predisposes the problems causing local skin irritation, inflammation, and ulceration and encouraging secondary infection [8].

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that play a crucial role in remodeling connective tissue and promoting wound healing but when excessive, they may exacerbate the skin lesion by degrading the extracellular matrix which is important to maintain normal skin structure. Thus the inhibition of these enzymes seems to contribute to reduce inflammation and ulceration [9, 11].

Minocycline is a broad spectrum antibiotic that is associated with the tetracycline family, and aside from their antimicrobial effects as described previously [11], it chelates calcium and directly inhibits collagenolytic enzymes including matrix MMPs, elastase and cathepsins. As overproduction of these enzymes is possible in calcinosis cutis, the inhibition of these enzymes is important in reducing inflammation and ulceration [10, 11]. In addition, the calcium chelating ability of tetracyclines is well known in light of decreased size of the calcium salt deposits [10]. Thus, it is likely that the action of minocycline is also relevant. In

human medicine, minocycline was proved useful in treating cutaneous calcinosis in limited cutaneous systemic sclerosis [10]. Also in rodent models, minocycline was proved to be helpful in prevention of calcium accumulation by inhibiting aortic calcification which was associated with MMP mediated elastin degradation. The study results imply that the role of minocycline may be beneficial for dogs with calcium accumulation disorders [7].

In this case, dystrophic calcinosis cutis is thought to be related with iatrogenic HAC, a form of dystrophic calcification resulting in deposition of calcium salts on dermal collagen and elastin fibers, with no systemic disturbance in calcium or phosphorus metabolism being detectable. Discontinuation of the steroid did not improve the skin lesions, so we applied minocycline for the purpose of alleviating the lesions of calcinosis cutis and found that there were improvement in reduction in size of calcinosis deposit and resolution of erythema located in the area of calcinosis cutis.

Although the effectiveness of minocycline for calcinosis cutis would remain unknown until many studies are conducted with large scales, this case suggests that there might be a beneficial effect of minocycline in the treatment of calcinosis cutis induced by iatrogenic HAC.

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