Calcinosis Cutis, Calcinosis Circumscripta, and “Mille Feuille” Lesions

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Skin and subcutaneous lesions of 2 cases with natural occurring Cushing’s disease and 1 case with calcinosis circumscripta were compared. Case 1 was typical of osteoma cutis, containing somewhat regularly arranged discrete ossification foci in the mid and deep dermis. Case 2 had layers of “mille feuille”, yellowish to white gritty substances diffusely scattered in the subcutis, seen histologically as disseminatedly scattered light purple crystalloid and blue granular mineral salts. Lesions stained orange red with Alizarin Red S indicated the presence of calcium ions. Discrete ossification foci in the deep dermis and early multifocal collagenolysis with mineralization were also noted. Case 3 was typical of calcinosis circumscripta, seen grossly as yellowish chalky substance in both dermis and subcutis, and histologically as lakes of well-circumscribed light purple crystals and granular deep blue mineral salts. Case 2 had features of calcinosis cutis such as ossification foci and early multifocal collagenolysis. Case 2 also had “mille feuille” that was histologically similar to those mineral salts in case 3, but was not circumscribed, and was not exactly calcinosis universalis. The component in case 1 was most likely hydroxyapatite Ca10(PO4)6(OH)2; the “mille feuille” of case 2 was most likely “calcium soap” after panniculitis and fat necrosis; and that in case 3 was most likely calcium phosphate CaPO4. Local factors, such as fluid exudation reflecting how well the inflammation was controlled clinically, may influence the wound healing, and thus the outcome of lesions.

Key Words: calcinosis, calcification, mille feuille, Cushing’s disease, renal failure, Alizarin red S

Introduction

Calcinosis cutis is commonly seen in dogs with naturally occurring hyperadrenocorticism (Cushing’s disease). Calcinosis circumscripta is a clinically distinct subgroup of calcinosis cutis characterized by focal or multifocal deposition of mineral salts usually in the subcutis and grossly as more or less tumoral nodules. The mechanisms of calcification are divided into four categories: dystrophic, metastatic, idiopathic, and iatrogenic. The components of mineral deposits may also differ, some being calcium phosphate CaPO4 and others being hydroxyapatite Ca10(PO4)6(OH)2. In human skin calcification, CaCO3 and type B carbonate hydroxyapatite have also been recorded. In case of fat sponification such as that occurring in the subcutis, combination of fatty acid with calcium results in so-called “calcium soap”, but whether other ions are deposited over the calcium soap is usually not identified. In humans, some common conditions for dystrophic calcification are connective tissue disorders, panniculitis, various inherited disorders, neoplasms, infection by especially parasites, and focal trauma, while in dogs, it is most often associated with hyperadrenocorticism (C. cutis) and focal trauma (C. circumscripta). One of the most common conditions for metastatic calcification in humans, dogs and cats is chronic renal failure, and in addition hypervitaminosis D and neoplasms associated with bony destruction such as lymphoma and multiple myeloma. A number of iatrogenic and idiopathic calcifications occur in conditions such as percutaneous absorption of products containing calcium chloride or calcium carbonate, subcutaneous administration of calcium gluconate, with the use of

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amphotericin B, pentazocine and pitressin tannate indicated.2, 4-5, 17 Dystrophic calcification is thought to be initiated by the deposition of phosphate ions onto a collagenous or elastic matrix.4-5, 17 The matrix may be derived from a focal onsite collagenolysis or pathological fibrosis subsequent to a local inflammation. Metastatic calcification involves the precipitation of calcium salts in normal tissue. Overlaps or more than one mechanism may occur in any particular single case. In this report, we describe cases typical of calcinosis cutis and calcinosis circumscripta, and discuss how intermediate lesions such as “mille feuille” result.

Case Report

Case 1. A 10-year-old male obese large size pointer had had a 3-month period of pruritus, and multi-local areas of alopecia on the back and shoulder regions. The skin was firm, and a biopsy was taken from the left shoulder with a 5 x 10 cm lesion. Calcinosis cutis of Cushing’s disease was suspected.

Case 2. A 6-year-old male Golden Retriever had been diagnosed with Cushing’s disease, based on a pendulous abdomen and a poorly healed wound on the left shoulder. Recently the patient was submitted for castration. On physical examination, three firm and moveable masses were noted. Two masses, of 3 x 1.5 x 1 cm and 7 x 2 x 1 cm respectively, had been noted on the dorsal neck area for months (per owner) after the dermatitis recovery (see above). A 3rd mass of 7 x 2 x 1.5 cm was noted on the dorsal root of the tail for more than 2 weeks before the recent admission. Grossly, these 3 masses did not invade the underlying skeletal muscle.

Case 3. A 3-year-old male German Shepherd, of 25.1 kg body weight, was presented with a 1 week history of anorexia, vomiting, lethargy, and intermittent seizures. At presentation, the dog was severely emaciated and comatous with 1 episode of convulsion. Physical examination revealed hyperthermia (Body temperature 40.8°C), moderate pale oral and ocular mucosae, 8% dehydration, halitosis, and tachypnea. No abnormality was found on hair coat except for multiple yellow fixed firm nodules on all pawpads. A biopsy of the pad’s nodules yielded a diagnosis of Calcinosi circumscripta. Hematology revealed non-regenerative normocytic hyperchromic anemia and leukocytosis, characterized by neutrophilia without left shift and lymphopenia (Table 1). Blood chemistry showed marked azotemia, elevated alanine aminotransferase, and hyperglycemia. Electrolyte imbalances of hypocalcemia, hyperphosphatemia, hyponatraemia, and hypochloremia were also present (Table 2).

Hemodialysis (HD) was performed to alleviate the life-threatening azotemia. After the first HD, the dog was responsive, able to eat, to stand up, and to walk, but exhibited a swaying back. During the 11 days of hospitalization, five HDs were performed at 1, 3 and 5 day intervals, in addition to the daily intravenous fluid therapy. Erythropoietin was also applied to remedy the markedly reduced PCV after HD. The dog was alert, active, and without further seizures and was subsequently discharged. Three days later, the dog was reportedly anorexic, lethargic, and dull but responsive. Hematology and blood chemistry (Tables 1, 2) revealed non-regenerative anemia, leukocytosis with neutrophilia, marked azotemia, mild hypoalbuminemia, hyperphosphatemia, hyperkalemia, and hyponatraemia. Because of the poor prognosis and high cost of further HD, the animal was euthanatized, and a necropsy was performed.

Pathology

Case 1. Subgrossly, there were several discrete ossification foci arranged somewhat regularly located in the mid and deep dermis (Figure 1). The ossification foci were roughly aligned at the isthmic level of the hair follicles where the
### Table 1. Routine hematology of patient case 3 during the clinical course

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1 (1st presentation)</th>
<th>Day 11 (Discharged)</th>
<th>Day 14 (2nd visit)</th>
<th>Reference values&lt;sup&gt;10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells (x 10&lt;sup&gt;6&lt;/sup&gt;/µL)</td>
<td>4.04</td>
<td>1.98</td>
<td>2.04</td>
<td>4.95-7.87</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.7</td>
<td>5.3</td>
<td>5.4</td>
<td>11.9-18.9</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>28.6</td>
<td>13.6</td>
<td>14.4</td>
<td>35-57</td>
</tr>
<tr>
<td>MCV (µm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>70.8</td>
<td>68.7</td>
<td>70.6</td>
<td>66-77</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>37.4</td>
<td>39</td>
<td>37.5</td>
<td>32-36.3</td>
</tr>
<tr>
<td>White blood cells (n/µL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>93</td>
<td>97</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Neutrophils (n/µL)</td>
<td>20460</td>
<td>19206</td>
<td>37018</td>
<td>2900-12000</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (n/µL)</td>
<td>440</td>
<td>396</td>
<td>2230</td>
<td>400-2900</td>
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<tr>
<td>Monocytes (%)</td>
<td>5</td>
<td>1</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Monocytes (n/µL)</td>
<td>1100</td>
<td>198</td>
<td>5352</td>
<td>100-1400</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0-1300</td>
</tr>
<tr>
<td>Eosinophils (n/µL)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0-140</td>
</tr>
<tr>
<td>Basophils (n/µL)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Platelets (x 10&lt;sup&gt;3&lt;/sup&gt;/µL)</td>
<td>294</td>
<td>244</td>
<td>-</td>
<td>211-621</td>
</tr>
<tr>
<td>RPI</td>
<td>0.4</td>
<td>-</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

MCV, Mean corpuscular volume; MCHC, Mean corpuscular hemoglobin concentration; RPI, Reticulocyte production index.

### Table 2. Blood chemistry of the patient case 3 during the clinical course

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day 1 (1st presentation)</th>
<th>Day 11 (Discharged)</th>
<th>Day 14 (2nd visit)</th>
<th>Reference values&lt;sup&gt;10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total plasma protein (g/dL)</td>
<td>6.9</td>
<td>-</td>
<td>6.2</td>
<td>6.0-7.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.2</td>
<td>2.4</td>
<td>2.2</td>
<td>2.3-3.1</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>276</td>
<td>195</td>
<td>71</td>
<td>10-109</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>55</td>
<td>-</td>
<td>92</td>
<td>13-15</td>
</tr>
<tr>
<td>ALKP (U/L)</td>
<td>41</td>
<td>-</td>
<td>122</td>
<td>1-114</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>228</td>
<td>75</td>
<td>129</td>
<td>76-119</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>378</td>
<td>62</td>
<td>157</td>
<td>8-28</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>15.4</td>
<td>8.6</td>
<td>11.4</td>
<td>0.5-1.7</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.6</td>
<td>12.2</td>
<td>11.8</td>
<td>9.1-11.7</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>40.9</td>
<td>19.6</td>
<td>25.6</td>
<td>2.9-5.3</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>127</td>
<td>143</td>
<td>136</td>
<td>142-152</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.9</td>
<td>4.4</td>
<td>5.3</td>
<td>3.9-5.1</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>81</td>
<td>101</td>
<td>102</td>
<td>110-124</td>
</tr>
</tbody>
</table>

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALKP, Alkaline phosphatase; BUN, blood urea nitrogen.
sebaceous duct and arrector pili muscles normally joined the hair follicles; and in the deep dermis at the level where the sweat glands normally originated. Histological lesions were typical of “osteoma cutis” (Figure 2) surrounded by fibrosis with little to no inflammation. Occasionally, adjacent hair follicles were cystically dilated and surrounded by inflammatory cells (perifolliculitis), mainly plasma cells, which extended to the epidermis, which was focally ulcerated. The atrophy of the epidermis was not apparent. The number of hair follicles was severely reduced, consistent with alopecia seen clinically. The sebaceous glands and the arrector pili muscle were atrophic and reduced in number, as was the number of sweat glands. The atrophy of dermal collagen was more apparent in the deep dermis.

Case 2. Grossly, the specimens were gritty and difficult to slice smoothly. They contained layers of yellow chalky substance (Figure 3) present as either “mille feuille” like (Figure 4) or only very rarely a circumscribed mass (Figure 4). Histologically, there was a layer of discrete ossification foci aligned in the deep dermis (Figure 4) that appeared to arise from the center of focal fibrosis with little to no inflammation. The epidermis was severely atrophic, and the number of hair follicles was not apparently reduced, but a few of them had follicular keratosis. The pores of the hair follicle were not open as in “comedone”. The number of sweat glands was reduced, and most of them were empty but cystically dilated and lined by atrophic epithelium. The atrophy of dermal collagen was evidenced by increased space between fibers. In the subcutis, calcinosis was present in 2 forms with hematoxylin and eosin stain. One form was light purple crystals of variable sizes and shape, ranging from 10 μm in diameter to 250 μm in length or 100 μm in width. The other form was in blue granular minerals (Figure 4). These mineral salts were widely scattered among a background of fibrosis with plump fibroblasts mixed with inflammatory cells which were previously neutrophilic. Only occasionally were these materials incompletely circumscribed by fibrous tissue. These mineral salts interspersed with necrotic adipose tissue, from which they were likely derived by saponification. Elsewhere, dermal collagen fibers appeared to be multifocally hypereosinophilic and disrupted with basophilic mineralization (Figure 5). Alizarin Red S, indi-
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Case 1. Three skin biopsies from case 1 showing layers of yellow gritty materials present in the dermis and “mille feuille” in the subcutis.

Figure 3 — Three skin biopsies from case 2 showing layers of yellow gritty materials present in the dermis and “mille feuille” in the subcutis.

Figure 4 — Subgross of a skin biopsy from case 2 showing relatively discrete foci of ossification (arrowheads) in the deep dermis and disseminatedly scattered mineral salts (arrows), mimicking “mille feuille” grossly, in the subcutis. Hematoxylin and eosin stain.

Figure 5 — Early foci of collagenolysis with subsequent mineralization are present in the dermis of case 2. Hematoxylin and eosin stain.

cative of the presence of calcium ions, was noted multifocally in both dermis and subcutis (Figure 6). The lesions of all three specimens appeared similar.

Case 3. Grossly, lesions dorsal and lateral to the digital, metacarpal as well as metacarpal pads of all four paws appeared swollen, with the left forefoot being most severely affected (Figures 7 and 8). The left forefoot swelled to 5.5 x 4 x 4 cm, followed by the right forefoot at 4.25 x 3 x 3 cm, and both hindfeet at 2.3 x 2 x 2 cm. Upon dissection, the two lateral lobes$^{13}$ of the heart-shaped metacarpal pads contained firm swelling with mildly erosive skin, while most of the central apex distal of the pad was largely spared (Figure 8). They contained multiple white chalky firm nodules of various sizes. Lesions in the forefeet were generally more severe than those of the hindfeet. Histologically, there were multifocal epidermal ulcerations with transepidermal and/or transfollicular elimination of minerals accompanied by formation of granulation tissue. The skin adnexa were mostly absent. Numerous lakes of well-circumscribed light purple crystal and blue granular minerals were scattered throughout, from the dermis to the subcutis (Figure 9), in a background of fibrosis at different stages of maturation. Light purple crystals appeared mostly at the peripheral and blue granular minerals in the center (Figure 10). These lakes of minerals were encapsulated with either normal residual collagen or elastic fibers in the subcutis or those derived from pathologic fibrosis with variable degrees of inflammation containing mostly mononuclear cells and multinucleated macrophages.

Interestingly, a blind fistula (Figure 9) or sinus containing numerous neutrophils developed in between lakes of well-circumscribed minerals. Light purple crystals were deposited regularly along the fistula wall with purulent inflammation and granulation tissue. The epidermal opening of the fistula was not found.

Elsewhere the renal cortices were pale and firm bilaterally. The pericardial
Figure 6 — A section from case 2 stained orange red with Alizarin Red S indicative of the deposition of calcium ions onto the lesions. Alizarin Red stain.

Figure 7 — Severe swelling of left and right fore-paws in case 3 affected with calcinosis circumscripta.

Figure 8 — Yellow chalky nodular materials are present in the dermis and subcutis of a paw from case 3. The two lateral lobes of metacarpal pad are more severely affected, while the apex distal (*) is relatively spared.

Figure 9 — Subgross of a section from case 3 showing well-circumscribed lakes of light purples crystalloid and blue granular mineral salts present in the dermis and subcutis. Note also a blind fistula (*) with purulent inflammation without apparent outer opening. Hematoxylin and eosin stain.

Figure 10 — Well-circumscribed lakes of mineral salts are present in the dermis (arrowheads) and subcutis (*). Hematoxylin and eosin stain.
cavity was filled with 13 ml of red cloudy (fibrinopurulent and hemorrhagic) exudate with adhesions, and the left ventricular walls were severely hypertrophic. The jugular vein, right ventricle, and pulmonary artery were filled with chicken fat clots. These cardiovascular lesions were likely caused by improper catheterization for HDs done in another clinic before admission to the NTU veterinary hospital. The lung was slightly edematous and emphysematous, and otherwise unremarkable.

Histological examination confirmed chronic renal failure. There was a severe diffuse chronic nephritis characterized by diffuse fibrosis with a moderate lymphocyte infiltration in the interstitium and along the pelvis. Most glomeruli were atrophic or obsolete, with dilated Bowman’s spaces, and thickened sclerotic and mineralized Bowman’s capsule. Tubular basement membranes were mineralized along with mineral salts within tubular lumens. Segmental mineralization also occurred on the arterial walls. Multifocal areas of amyloidosis were suspected. In the heart, organized fibrinous exudates mixed with neutrophils and mononuclear cells covered the epicardium and extended into epicardial adipose tissue and myocardium of the subepicardial region. In the stomach, multiple thrombi were present within vascular lumens of the mucosa, and mineralization occurred predominantly in the mid mucosa, without the tissue destruction suggestive of metastatic mineralization. In the liver, there was a diffuse moderate atrophy of centrilobular hepatic cords with intracellular brown pigments, and with dilated central and portal veins consistent with subacute to chronic passive congestion. In the lung, there was moderate diffuse alveolar emphysema, and some alveolar septae were expanded by fresh and lysed RBCs, consistent with passive congestion. There was no alveolar calcinosis, as would be expected in uremic dogs. The spleen was moderately atrophic with a significant increase of coarsely granular pigments (hemosiderin) in the red pulp, consistent with passive congestion.

The internal parathyroid gland appeared to be hyperplastic, mainly of light cells, and was considered secondary to chronic renal failure. Other organs, including the thyroid, intestine, pancreas, skin, and skeletal muscle, were unremarkable.

Discussion

The mechanism of skin calcinosis is divided into dystrophic, metastatic, iatrogenic and idiopathic types. In case 1, the location of ossification foci were somewhat regular (Figures 1 and 2), indicative of an association with skin adnexa, such as the sweat gland, where dystrophic calcification is likely to exist, since inflammation of mainly plasma cells was found. The sweat gland is where calcium is heavily excreted and where metastatic calcification is found preferably located in human case of calcinosis. Thus, the finding of ossification foci in these specific locations was not an accident (Figures 1, 2, and 4). Because of the presence of bone (Figures 1 and 2), its component was most likely hydroxyapatite Ca10(PO4)6(OH)2. In case 2, ossification foci in the deep dermis appeared to be dystrophic, since they arose from the center of focal fibrosis (metaplastic bone) and its component was also probably hydroxyapatite (Figure 4). The “mille feuille” lesions in the subcutis of case 2 were of dystrophic subsequent to panniculitis and was thus most likely calcium soap.

Calcinosis circumscripta involving multiple pawpads has been linked to chronic renal failure as occurred in case 3, manifested by hyperphosphatemia and hypocalcemia (Table 2), and histologically parathyroid hyperplasia. These paws were also where repeated traumas were likely to occur, as manifested by the fistula (purulent inflammation) found (Figure 9), indicative a dystrophic mechanism. However, without a metastatic mechanism, one would not expect to see such an extensive scale of calcium deposition. In case 3, the metastatic calcification was also mani-
fested in mineralization of the gastric mu-
cosa and kidney, but not in the lung.

It is speculated that local conditions
where calcium ion deposits may determine
the outcome of lesions. For example,
chronic plasmacytic inflammation without
fluid exudation, such as seen in case 1 and
in the deep dermis of case 2, favored ossi-
fication. Although fat lysis and subsequent
saponification or metastatic calcification
favors the formation of circumscribed le-
sions, as seen in case 3 (Figures 8-10), the
residual collagen or elastic fiber and tissue
of pathologic fibrosis served well as the
capsule for circumscription, despite a pu-
rulent inflammation (Figure 9). However,
in case 2, the layered arrangement of adi-
pose tissue together with a neutrophilic in-
flammation (liquefactive necrosis) with the
formation of immature fibrous tissue re-
resulted in “mille feuillev lesions. These
“mille feuillev lesions may be easily con-
fused with the so called “calcinosi универ-
salis”, which in its original definition in-
cludes calcification of the muscle and ten-
don.14-15 Therefore, it is likely that in a
background of mature fibrous tissue, with
little or no inflammation, and with little
exudation, ossification will result, as in
case 1. In a background of mature fibrous
tissue, with little or no inflammation, with
fluidity from lipolysis, circumscribed le-
sions will result, such as in case 3. In a
background of immature fibrous tissue
mixed with uncontrolled purulent inflam-
mation, on the other hand, a “mille feuille”
lesion will likely result, as seen in case 2.
Thus local fluid exudation and how well
the inflammation is controlled clinically
seemed important in influencing the
growth of fibrous tissue (wound healing,
see below), and thus the outcome of le-
sions.

The atrophy of epidermis, dermal col-
lagen, and skin adnexa caused by the com-
bined functional disturbances in protein
catabolism, lipolysis, gluconeogenesis, and
anti-inflammatory effects of glucocorticoid
was variably seen, but not overall, in case
1 and 2.6,8,11 Additional factors such as
idiosyncracy may also contribute to the
outcome of lesions. These functional dis-
turbances will determine the wound heal-
ing and how the inflammation progresses,
and thus how the calcified lesions are
formed. It was also hypothesized that local
elevation in alkaline phosphatase activity
can lead to hydrolysis of extracellular py-
rophosphatase, which normally inhibits
calcium deposition.16 Further local tissue
injuries can increase cell membrane per-
meability, allowing cytosolic influx of cal-
cium, and can lead to the precipitation of
cytosolic CaPO4.4-5,16-17 The same me-
chanisms could occur in the hypercalcemia
and hyperphosphatemia setting. In both
cases 1 and 2, the blood calcium and phos-
phorus levels were unknown, but most
likely normal. In case 3, the [Ca x P] solu-
bility product ranged between 238 and 310
(rows 10-11, Table 2), far beyond the >70
threshold for precipitation.4-5

The presence of calcium carbonate
CaCO3 in skin calcification is interesting.14
Type B carbonate hydroxyapatite together
with collagen and β-carotene had also
been characterized in skin calcified depo-
sit.9 Type B carbonate hydroxyapatite is
that wherein CO3-2 occupies the PO4-3
anionic site. Theoretically, only organs or
systems involved in the acid-base balance,
such as the blood, lung, kidney, and the
gastric mucosa, have local sources of
HCO3-7,12 and only in dysregulation status
could these anions be made available dur-
ing the calcification process. These sites
are also where calcification is commonly
seen in uremic dogs, such as that in case 3.
Whether these HCO3- were available in the
skin for acid-base homeostasis is not
known, but it is clear that calcium is abun-
dant there locally.1

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References


