Metastatic calcinosis (including calcinosis cutis) in a young dog with multiple urinary tract abnormalities

Arnaud Muller*, Frédérique Degorce-Rubiales† and Eric Guaguère*

*Clinique Vétérinaire Saint-Bernard, 598 avenue de Dunkerque, F-59160 Lomme, France
†Laboratoire d’Anatomie Pathologique du Sud-Ouest, 129 route de Blagnac, F-31201 Toulouse, France
Correspondence: Arnaud Muller, Clinique Vétérinaire Saint-Bernard, 598 avenue de Dunkerque, F-59160 Lomme, France.
E-mail: camuller@free.fr

Sources of Funding
This study is self-funded.

Conflict of Interest
No conflicts of interest have been declared.

Abstract

Metastatic calcinosis associated with chronic renal failure and multiple urinary tract abnormalities was diagnosed in a 6-month-old Brittany spaniel that was presented with calcinosis cutis. This case report highlights the importance of skin as an indicator of systemic disease. The aetiopathogenesis of the four main types of tissue calcification is defined and discussed with an emphasis on metastatic calcinosis.

Accepted 2 June 2010

Introduction

Calcification is defined as calcium deposition in tissue.1 The term calcinosis cutis is used when the deposition affects the dermis (in particular collagen fibres) and subcutaneous tissues. Calcium salts exist as carbonates or phosphates, but are mostly comprised of hydroxyapatite (Ca$_5$(PO$_4$_)$_3$OH)$_2$.2–4 Cutaneous calcinosis may be dystrophic, metastatic, iatrogenic or idiopathic (Table 1). Idiopathic calcinosis circumscripta is the most common type.4–17

This report documents a case of metastatic calcinosis cutis in a dog associated with multiple congenital urinary abnormalities.

Case report

A 6-month-old female Brittany spaniel with a history of poor appetite, polyuria and polydipsia was referred with pruritic skin lesions of one month’s duration. Water intake was estimated at 2 L/day (normal intake ~0.6 L/day), and the urine specific gravity was 1.010. The dog was thin and in poor condition. In addition, the dog was small and underweight (12 kg) for her age and breed. The dog was not dehydrated, and the mucous membranes were pale. The urinary bladder was unusually hard but did not appear painful on palpation. Cutaneous lesions consisted of numerous papules and plaques confined to the dorsum of the muzzle, forehead, legs and ventral abdomen (Figure 1a,b). The lesions were mostly erythematous, erosive or ulcerated, and were occasionally covered by crusts. Differential diagnoses included cutaneous calcinosis (cutaneous lesions and possible renal disease), demodicosis, eosinophilic furunculosis, bacterial furunculosis and acral lick dermatitis.

Skin scrapings were negative for demodicosis. Cytological examination of impression smears from ulcerated/crusted lesions revealed mixed inflammation (healthy or degenerate neutrophils and macrophages) with free coci (suggestive of Staphylococcus spp.) typical of secondary pyoderma. Histopathological examination of five 6 mm formalin-fixed punch biopsies from lesional skin revealed moderate epidermal thickening (regular acanthosis) and focal ulcerations with thin crusts (Figure 2). The dermal architecture was extensively disrupted by diffuse granulomatous inflammation, with a diffuse infiltrate of histiocytic, epithelioid-type macrophages and multinucleated giant cells encircling intragranuloclastic granular material typical of mineralized collagen (Figure 3). Von Kossa’s stain confirmed calcium deposition within the dermis (Figure 4). The histopathological diagnosis was calcinosis cutis.

Urinary analysis (collected by cystocentesis) revealed mild (+) proteinuria (Combur$^®$ test, Roche), pyuria (more than five leukocytes per high dry objective field, although bacterial culture was not performed), hypos thenuria (specific gravity 1.010) and crystaluria (calcium oxalate crystals on morphology). Haematological and biochemical profiles confirmed a normocytic normochromic anaemia (haematocrit, 0.33 L/L; and haemoglobin, 105 g/L (reference values, 120–180 g/L)) and severe renal failure (blood urea nitrogen, >45.9 mmol/L (reference values, 2.5–9.6 mmol/L); and creatinine, 16,619 mmol/L (reference values, 442–1591 mmol/L); calcium, 324 mmol/L (reference values, 197–299 mmol/L); and phosphorus, 2.52 mmol/L (reference values, 0.81–2.20 mmol/L). The calcium–phosphorus product was 816 (reference values, 360 mmol$^2$/L$^2$).

Abdominal radiography demonstrated a calcified bladder wall. Iodine cystography revealed an abnormal image with a cranial diverticulum, strongly suggestive of a patent urachus (Figure 5).

No clinical or biochemical improvement was observed after 3 days of diuresis with 0.9% saline infusion and treatment with cefalexin (30 mg/kg/day) for pyoderma and pyurria, suggesting irreversible renal failure. In light of
Table 1. Classification of cutaneous calcinoses in domestic carnivores (see text for references)

<table>
<thead>
<tr>
<th>Type of Calcinoses</th>
<th>Pathogenesis and Underlying Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystrophic calcinoses</td>
<td>Local tissue degradation (skin) in the absence of abnormal calcium and phosphorus metabolism. Underlying or associated conditions: Hyperadrenocorticism, Diabetic mellitus, Local inflammation, Tissue degeneration or necrosis, Cutaneous tumour.</td>
</tr>
<tr>
<td>Metastatic calcinoses</td>
<td>Abnormal calcium and phosphorus metabolism. Underlying or associated conditions: Chronic renal failure, Primary hyperparathyroidism, Pseudohyperparathyroidism, Hyperparathyroidism D, Hypercalcemia of malignancy, Unknown cause.</td>
</tr>
<tr>
<td>Idiopathic calcinoses (calcinosis universalis and true calcinosis circumscripta)</td>
<td>Unknown mechanism (probable tissue damage).</td>
</tr>
<tr>
<td>Iatrogenic calcinoses</td>
<td>Percutaneous absorption of calcium. Underlying or associated conditions: Calcium gluconate injection, Percutaneous penetration of calcium chloride, Injection of progestagens, Polydioxanone sutures.</td>
</tr>
</tbody>
</table>

Figure 1. Erythematous, erosive and ulcerated papules and plaques on the muzzle (a) and dorsal forepaw (b) of a 6-month-old female Brittany spaniel with metastatic calcinosis from chronic renal failure. Note the similarity of the lesion on this dog’s paw to acral lick dermatitis.

Figure 2. Low-magnification photomicrograph of calcinosis cutis in a 6-month-old female Brittany spaniel with metastatic calcinoses from chronic renal failure, illustrating epidermal acanthosis and diffuse granulomatous dermatitis with intratresional basophilic granular material typical of mineralized collagen (4 µm tissue section, formalin fixed, haematoxylin and eosin stained, x200).

Figure 3. Granulomatous reaction comprised of histiocytes cells organized around basophilic mineral deposits (calcium salts) (4 µm tissue section, formalin fixed, haematoxylin and eosin stained, x200).

Figure 4. Calcium deposits within the dermis (4 µm tissue section, formalin fixed, Von Kossa stained, x25).
the poor prognosis of the renal failure, the dog was euthanased, and necropsy revealed multiple congenital urinary abnormalities: severe bilateral hydronephrosis, bilateral megaureters and patent urachus. The bladder wall was grossly thickened, firm and calcified (Figure 6). Histopathology revealed calcium deposits within the bladder wall and kidneys (nephrocalcinosis with chronic interstitial nephritis), but not in the lungs, heart, liver, spleen or footpads. The definitive diagnosis was metastatic calcinosis caused by chronic renal failure secondary to congenital urinary abnormalities.

Discussion

Chronic renal failure (with secondary hyperparathyroidism and hypercalcaemia and/or hyperphosphataemia) is the most frequent cause of metastatic calcinosis in dogs. Metastatic calcinosis is extremely rare in dogs, although it is more frequent in cats. In dogs, it has been previously described in association with chronic renal failure, particularly with renal dysplasia in the shih tsu and Lhasa apso, with primary hyperparathyroidism (abnormal increased secretion of parathyroid hormone) and hypervitaminosis D. To our knowledge, this report is the first case of metastatic calcinosis associated with multiple congenital urinary abnormalities in a dog.

The likelihood of metastatic calcification increases when the serum product of the calcium–phosphorus concentration exceeds 560 (concentrations expressed in mmoles per litre) or 70 (concentrations expressed in milligrams per decilitre). The corresponding reference values are 360 and 45, respectively. These levels can be achieved by isolated increases in phosphorus or calcium, or by a simultaneous increase in both. Metastatic calcification involves several mediators, particularly parathyroid hormone (causing hypophosphataemia and hypercalcaemia) and vitamin D (causing hypercalcaemia and hyperphosphataemia). In chronic renal failure, hyperphosphataemia and decreased vitamin D synthesis induce a secondary hyperparathyroidism and occasionally hypercalcaemia (in 3–14% of cases). When the calcium–phosphorus product exceeds 560 (the product in this case was 816), calcium deposits can appear in soft tissues (e.g. the skin, kidneys, bladder, blood vessels, lungs and elsewhere; Figure 7). In humans, metastatic calcinosis is most commonly observed in lymphoma, multiple myeloma, metastatic carcinoma (pseudohyperparathyroidism with paraneoplastic hypercalcaemia due to a parathyroid hormone-like substance secreted by the tumour) or osteolysis.

Cutaneous calcinosis is most frequently characterized by solitary to multicentric, firm, erythematous and painful papules, nodules or plaques, which progressively become ulcerated and crusted. The size of the lesions varies from
Muller et al.

0.5 to 8 cm in diameter (mean, 3 cm). Lesions may have a highly suggestive whitish or yellowish colour (indicating mineral deposition), with peripheral hyperpigmentation. These papules or nodules contain a whitish, sandy, chalky or pasty material. Mineralized material in the dermis may become more apparent after incising the skin but may be extruded through the skin in some individuals (especially in hyperadrenocorticism) through transepidermal or transfollicular elimination. This was not confirmed clinically or microscopically in our case. Calcinosis nodules are uni- or multiloculated, and transection demonstrates partition by fibrous septa. Sometimes the clinical lesions can be initially fluctuant (for example, in 44% of cases of calcinosis circumscripta), although they later become firmer, erythematous and ulcerated or crusted, as in our case. Differential diagnoses include acral lick dermatitis, furunculosis and pyotraumatic dermatitis, particularly as all these lesions may be pruritic and secondarily infected.

Cutaneous lesions associated with calcinosis can be solitary, localized to one body region or generalized. In metastatic calcinosis associated with chronic renal failure, skin lesions have always been reported in the footpads (although calcinosis of the pads can also be observed in idiopathic calcinosis circumscripta), except for one case of metatarsal metastatic calcinosis in a dog. The distribution of lesions in our case was unusual, because of the presence of multicentric clinical signs (i.e. dorsum of the muzzle, forehead, legs and ventral abdomen) without pedal lesions. In metastatic calcinosis, furthermore, cutaneous lesions are less commonly encountered than calcification of other soft tissues (e.g. kidney (nephrocalcinosis as in our case), lungs, blood vessels, heart and stomach).

Radiography of the footpads, skin and soft tissues can be useful to identify calcinosis, but definitive diagnosis requires histopathology of cutaneous lesional biopsies. Histopathological examination reveals large dermal or subcutaneous areas containing a granular substance that stains basophilic with haematoxylin and eosin stain and black with Von Kossa’s stain (the latter is normally only used when the deposits are very mild and difficult to detect). The mineralized foci are principally located along collagen and elastin dermal fibres. As in our case, the basophilic material is frequently surrounded by histiocytes, epithelioid cells and multinucleated giant cells. Other inflammatory cells, including lymphocytes, plasma cells and neutrophils, may also be present. There is often severe epidermal acanthosis, and the epidermis is sometimes ulcerated. If other histopathological (from sites not affected by calcinosis cutis) or clinical findings (e.g. history of glucocorticoid administration, polyphagia, polyuria–polydipsia, alopecia, pot-belly and cutaneous atrophy) are suggestive of endocrinopathy, hyperadrenocorticism has to be investigated. Senile perifollicular mineralization without pathological calcinosis, however, may be present in old poodles. Metastatic calcinosis is most frequently associated with chronic renal failure. A complete blood count and biochemistry analysis is therefore indicated when a cutaneous calcinosis is demonstrated.

Treatment of metastatic calcinosis may be curative (e.g. suppression of vitamin D in hypervitaminosis D) but more frequently is used to limit the development of other lesions by decreasing the calcium–phosphorus product. Treatment consists of a low-phosphorus diet (the classical nutritional recommendation in chronic renal failure) and phosphate binders (usually aluminium hydroxide, but magnesium hydroxide or ammonium chloride can also be given). This protocol can also be used to manage dystrophic calcinosis until the underlying disease is controlled. In one report of calcinosis associated with chronic renal failure in a dog, this treatment in addition to use of a charcoal absorbent (which has been shown in rats to maintain adequate excretion of phosphorus) resulted in complete resolution of footpad lesions (swelling and pain). In addition, the calcium–phosphorus product decreased from 585 to 337. Other drugs reported to be useful in the treatment of cutaneous calcinosis include the following: topical application of dimethylsulphoxide, which facilitates the transcutaneous elimination of calcium salts; diacetemiz, a calcium channel inhibitor that is cited in the human literature, although precise results are lacking; and intralesional glucocorticoids (e.g. methylprednisolone, triamcinolone), which could block inflammatory reactions and allow calcium absorption. In vitamin D toxicosis, furosemide (2–4 mg/kg three times a day per os) may be used to increase renal calcium excretion, and biphosphonate (pamidronate disodium, 1.3–2 mg/kg intravenously over 2 h) or salmon calcitonin (4–6 IU/kg three times a day subcutaneously) are used to inhibit calcium release from bone. When diuresis is necessary, 0.9% saline is preferred to reduce tubular reabsorption because it contains no calcium ions. In our case, however, the multiple urinary tract malformations and consequent renal failure were too severe to obtain any improvement of either the general condition or the cutaneous lesions.

References


