

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

Arnaud Muller*, Frédérique Degorce-Rubialest 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

Calcinosis 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 ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$).^{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 cocci (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 ulcers 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 intralésional basophilic 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.

Urine 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), hyposthenuria (specific gravity 1.010) and crystalluria (calcium oxalate crystals on morphology). Haematological and biochemical profiles confirmed a normocytic normochromic anaemia [haematocrit, 0.33 L/L (reference values, 0.37–0.55 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); creatinine, 16,619 $\mu\text{mol/L}$ (reference values, 442–1591 $\mu\text{mol/L}$); 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 pyuria, suggesting irreversible renal failure. In light of

Table 1. Classification of cutaneous calcinosis in domestic carnivores (see text for references)

	Primary pathogenesis	Underlying or associated conditions
Dystrophic calcinosis	Local tissue degradation (skin) in the absence of abnormal calcium and phosphorus metabolism	Hyperadrenocorticism Diabetes mellitus Local inflammation Tissue degeneration or necrosis Cutaneous tumour
Metastatic calcinosis	Abnormal calcium and phosphorus metabolism	Chronic renal failure Primary hyperparathyroidism Pseudohyperparathyroidism Hypervitaminosis D Hypercalcaemia of malignancy
Idiopathic calcinosis (calcinosis universalis and true calcinosis circumscripta)	Unknown mechanism (probable tissue damage)	Unknown cause
Iatrogenic calcinosis	Percutaneous absorption of calcium	Calcium gluconate injection Percutaneous penetration of calcium chloride Injection of progestagens Polydioxanone sutures

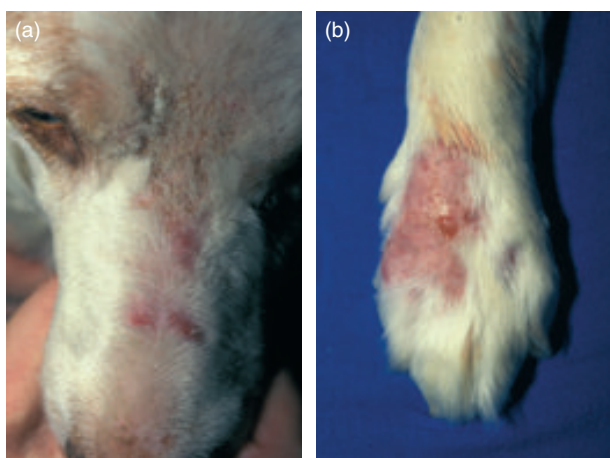


Figure 1. Erythematous, erosive and ulcerated papules and plaques on the muzzle (a) and dorsal forepaw (b) of a 6-month-old female Brittany spaniel with metastatic calcinosis from chronic renal failure. Note the similarity of the lesion on this dog's paw to acral lick dermatitis.

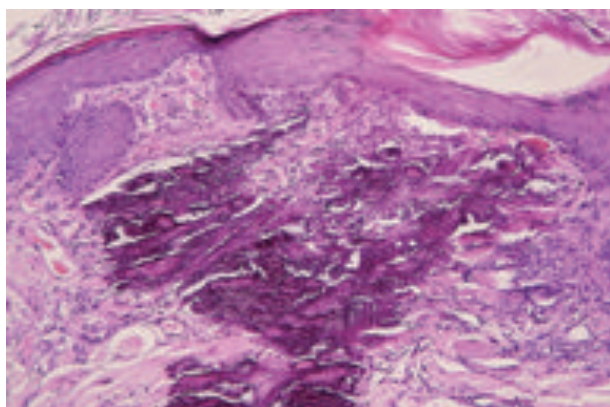


Figure 2. Low-magnification photomicrograph of calcinosis cutis in a 6-month-old female Brittany spaniel with metastatic calcinosis from chronic renal failure, illustrating epidermal acanthosis and diffuse granulomatous dermatitis with intralesional basophilic granular material typical of mineralized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

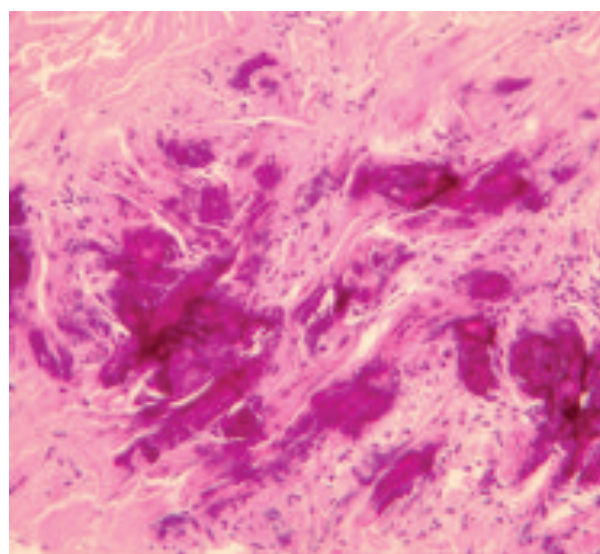


Figure 3. Granulomatous reaction comprised of histiocytes cells organized around basophilic mineral deposits (calcium salts) (4 µm tissue section, formalin fixed, haematoxylin and eosin stained, x200).

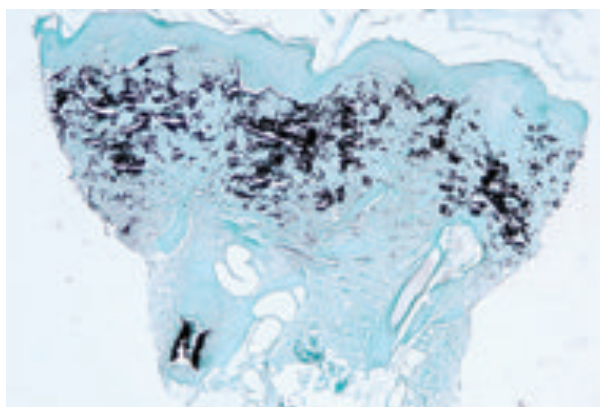


Figure 4. Calcium deposits within the dermis (4 µm tissue section, formalin fixed, Von Kossa stained, x25).

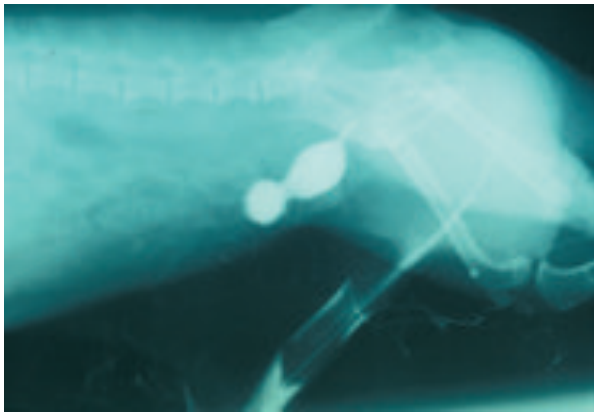


Figure 5. Contrast cystoradiograph showing a diverticulum at the cranial end of the urinary bladder consistent with a patent urachus.



Figure 6. Thickened and hard bladder wall and enlarged ureters found at post-mortem examination.

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.^{18–20} To our knowledge, this report is the first case of

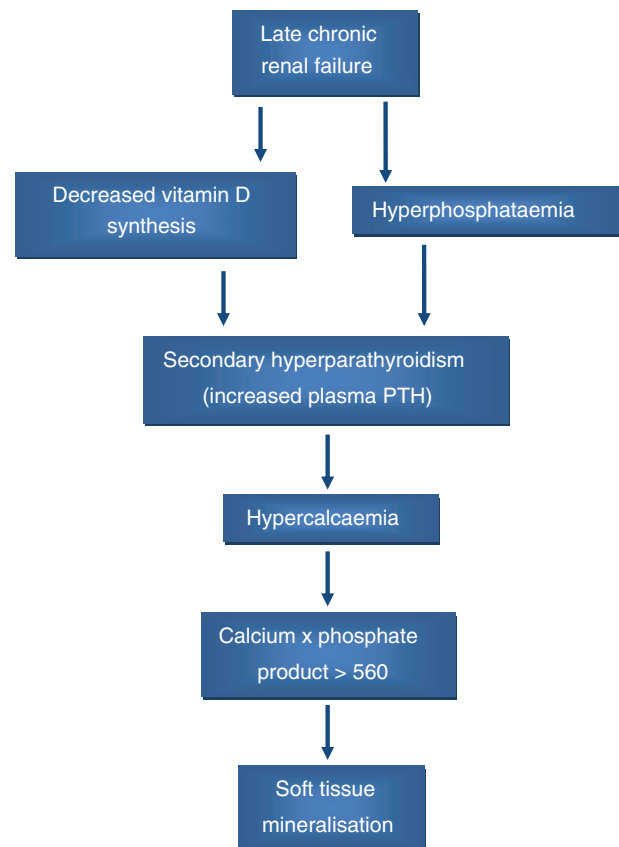


Figure 7. Pathophysiology of metastatic calcinosis in chronic renal failure.

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 mmol 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.^{21,22} 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).²³ 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.^{1,24}

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

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.²⁵ 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.^{17,26–28} 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.^{29–31} 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.^{32–34} Senile perifollicular mineralization without pathological calcinosis, however, may be present in old poodles.³⁵ 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).³⁶ 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; diltiazem, 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

1. Cribier B, Grosshans E. Calcinosis cutanées. *Annals of Dermatology and Venerology* 1992; 119: 151–68.
2. Alhaidari Z. La calcinose circonscrite du chien: à propos de deux cas. *Pratique Médicale et Chirurgicale de l'Animal de Compagnie* 1995; 30: 339–43.
3. Marcos R, Santos M, Oliveira J *et al.* Cytochemical detection of calcium in a case of calcinosis circumscripta in a dog. *Veterinary Clinical Pathology* 2006; 2: 239–42.
4. Curtis C. What is your diagnosis? (calcinosis circumscripta). *Journal of Small Animal Practice* 1994; 35: 444, 486.
5. Davidson EB, Schulz KS, Wisner ER *et al.* Calcinosis circumscripta of the thoracic wall in a German shepherd dog. *Journal of the American Animal Hospital Association* 1998; 34: 153–6.
6. Ginel P, Perez J, Rivas R *et al.* Calcinosis circumscripta associated with medroxyprogesterone in two poodle bitches. *Journal of the American Animal Hospital Association* 1992; 28: 391–4.
7. Ginel P, Lopez R, Rivas R *et al.* A further case of medroxyprogesterone acetate associated with calcinosis circumscripta in the dog. *Veterinary Record* 1995; 136: 44–5.
8. Gross TL. Calcinosis circumscripta and renal dysplasia in a dog. *Veterinary Dermatology* 1997; 8: 27–32.
9. Holahan ML, Loft KE, Swenson CL *et al.* Generalized calcinosis cutis associated with disseminated paecilomycosis in a dog. *Veterinary Dermatology* 2008; 6: 368–72.
10. Kirby BM, Knoll JS, Mandley PA *et al.* Calcinosis circumscripta associated with polydioxanone suture in two young dogs. *Veterinary Surgery* 1989; 18: 216–20.

11. Legendre AM, Dade AW. Calcinosis circumscripta in a dog. *Journal of the American Veterinary Medical Association* 1974; 164: 1192–4.
12. Munday JS, Bergen DJ, Roe WD. Generalized calcinosis associated with probable leptospirosis in a dog. *Veterinary Dermatology* 2005; 16: 401–6.
13. Paradis M, Scott DW. Calcinosis cutis secondary to percutaneous penetration of calcium carbonate in a dalmatian. *Canadian Veterinary Journal* 1989; 30: 57–9.
14. Ruopp JL. Primary hypoparathyroidism in a cat complicated by suspect iatrogenic calcinosis cutis. *Journal of the American Animal Hospital Association* 2001; 37: 370–3.
15. Schick MP, Schick RO, Richardson JA. Calcinosis cutis secondary to percutaneous penetration of calcium chloride in dogs. *Journal of the American Veterinary Medical Association* 1987; 191: 207–11.
16. Scott DW. Iatrogenic calcinosis cutis in a dog. *Veterinary Medicine and Small Animal Clinician* 1975; 70: 684–6.
17. Scott DW, Buerger RG. Idiopathic calcinosis circumscripta in the dog: a retrospective study of 130 cases. *Journal of the American Animal Hospital Association* 1988; 24: 651–8.
18. Declercq J, Bhatti S. Calcinosis involving multiple paws in a cat with chronic renal failure and in a cat with hyperthyroidism. *Veterinary Dermatology* 2005; 16: 74–8.
19. Nagode LA, Chew DJ. Nephrocalcinosis caused by hyperparathyroidism in progression of renal failure: treatment with calcitriol. *Seminars in Veterinary Medicine and Surgery: Small Animal* 1992; 7: 202–20.
20. Schaer M, Ginn PE, Fox LE *et al.* Severe calcinosis cutis associated with treatment of hypoparathyroidism in a dog. *Journal of the American Animal Hospital Association* 2001; 37: 364–9.
21. Feldman EC, Nelson RW. Hypercalcaemia and hyperparathyroidism. In: *Canine and Feline Endocrinology and Reproduction*, 3rd edn, Philadelphia, PA, W.B. Saunders, 2004: 355–96.
22. Morrow CK, Volmer PA. Hypercalcemia, hyperphosphatemia, and soft-tissue mineralization. *Compendium on Continuing Education: Small Animal* 2002; 24: 380–7.
23. Kruger J, Osborne C, Nachreiner R *et al.* Hypercalcemia and renal failure: etiology, pathophysiology, diagnosis, and treatment. *Veterinary Clinics of North America: Small Animal Practice* 1996; 26: 1417–46.
24. Cribier B. Calcinose et ossifications cutanées. In: Saurat JH, Laugier P, Grosshans E, *et al.*, eds. *Dermatologie et Maladies Sexuellement Transmissibles*, 3rd edn. Paris, Masson, 1999: 536–8.
25. Scott DW, Miller WH, Griffin CE. Calcinosis cutis. In: Muller and Kirk's *Small Animal Dermatology*, 6th edn. Philadelphia, PA: W.B. Saunders, 2001: 1398–9.
26. Guaguere E, Muller A, Magnol JP. Lésions cutanées associées à des maladies internes chez le chien. *Pratique Médicale et Chirurgicale de l'Animal de Compagnie* 1997; 32: 275–89.
27. Magnol JP, Cabanie P, Van Haverbeke G. La calcinose circonscrite du chien. *Revue de Medecin Veterinaire* 1977; 128: 1291–301.
28. Rook A, Wilkinson DS, Ebling FJG. Calcification and ossification of the skin. In: Champion RH, Burton JL, Burns T, *et al.*, eds. *Textbook of Dermatology*, 6th edn. Oxford, Wiley-Blackwell, 1998: 2663–6.
29. Joffe DJ. Calcinosis circumscripta in the footpad of a dog. *Canadian Veterinary Journal* 1996; 37: 161–2.
30. Kowalewich N, Hawkins EC. Calcinosis circumscripta involving the metatarsal region in a dog with chronic renal failure. *Canadian Veterinary Journal* 1992; 33: 465–6.
31. Stampley A, Bellah JR. Calcinosis circumscripta of the metacarpal pad in a dog. *Journal of the American Veterinary Medical Association* 1990; 196: 113–4.
32. Gross TL, Ihrke PJ, Walder EJ *et al.* Calcinosis cutis. In: *Skin Diseases of the Dog and Cat: Clinical and Histopathological Diagnosis*, 2nd edn. Oxford: Wiley-Blackwell, 2005: 373–7.
33. Tafti AK, Hanna P, Bourque AC. Calcinosis circumscripta in the dog: a retrospective pathological study. *Journal of Veterinary Medicine Series A –Physiology and Clinical Medicine* 2005; 52: 13–7.
34. Yager JA, Wilcock BP. Dermal changes. In: *Color Atlas and Text of Surgical Pathology of the Dog and Cat: Dermatopathology and Skin Tumors*. London: Mosby, 1994: 28–33.
35. Seaman WJ, Chang SH. Dermal perifollicular mineralization of Toy poodle bitches. *Veterinary Pathology* 1984; 21: 122–3.
36. Komori S, Washizu M. Metastatic calcinosis circumscripta treated with an oral charcoal absorbent in a dog. *Journal of Veterinary Medical Science* 2001; 63: 913–6.

Résumé Une calcinose métastatique associée à une insuffisance rénale chronique et à de multiples anomalies du tractus urinaire a été diagnostiquée chez un épagneul anglais de 6 mois présenté en consultation pour calcinose cutanée. Ce cas clinique souligne l'importance de la peau en tant que marqueur d'atteinte systémique. L'étiopathogénie des 4 principaux types de calcification tissulaire est définie et discutée avec une attention particulière pour la calcinose métastatique.

Resumen Se diagnosticó calcinosis metastática asociada con fallo renal crónico y anomalías múltiples del tracto urinario en un perro de raza Brittany Spaniel de seis meses de edad que se presentó con calcinosis cutis. Este caso ensalza la importancia de la piel como indicador de enfermedades sistémicas. Se define y discute la etiopatogénesis de los cuatro tipos principales de calcificación de tejidos con énfasis en la calcinosis metastática.

Zusammenfassung Eine metastatische Kalzinose, die mit chronischem Nierenversagen und mit multiplen Abnormalitäten des Harntrakts in Verbindung gebracht wurde, konnte bei einem 6 Monate alten Brittany Spaniel, der mit einer Calcinosis cutis präsentiert wurde, diagnostiziert werden. Dieser Fallbericht unterstreicht die Wichtigkeit der Haut als Indikator systemischer Erkrankung. Die Ätiopathogenese der vier Haupttypen der Gewebekalzifizierung wird definiert und mit dem Schwerpunkt metastatischer Kalzinose diskutiert.

要約 皮膚石灰沈着症との主訴で来院した6歳のブリタニースパニエルが、慢性腎不全と多発性尿路異常を併発した転移性石灰沈着症と診断された。この報告は皮膚が全身性疾患の指標として重要なことを強調するものである。主な4つのタイプの組織石灰化の原因病理論を定義し、転移性石灰沈着症を強調して述べた。