Clinicopathological findings in five cats with paw calcification

W Bertazzolo², L Toscani², S Calcaterra³, L, Crippa⁴, M Caniatti⁵, U Bonfanti⁶

This retrospective study describes the clinicopathological findings in five cats with soft tissue mineralisation of interdigital spaces and footpads. Paw disease was the reason for veterinary consultation in three out of five cats. All cats had laboratory findings suggestive of renal failure and high solubility product \([\text{calcium} \times \text{phosphorus}]\). In all cases, cytological examination of paw lesions was suggestive of calcinosis. The results of our study agree with two previous case reports of paw calcification in the cat, suggesting a metastatic pathogenesis and a correlation between paw mineralisation and renal failure.

© 2002 ESFM and AAFP. Published by Elsevier Science Ltd. All rights reserved.
Table 1. Signalment, history, principal clinical findings, follow-up and significant laboratory results in five cats with cutaneous calcinosis of paw

<table>
<thead>
<tr>
<th>Signalment</th>
<th>Cat 1</th>
<th>Cat 2</th>
<th>Cat 3</th>
<th>Cat 4</th>
<th>Cat 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLH, FS, 13y</td>
<td>Chronic renal failure diagnosed 6 months before. Generalised paw disease and lameness</td>
<td>Lameness, reluctant to move, progressive enlargement of all footpads, ulcerated interdigital nodules on all paws, anorexia and polyuria/polydipsia</td>
<td>Ulcerated nodules on paws noted two months before, anorexia and depression, polyuria/polydipsia</td>
<td>Progressive weight loss, anorexia and finally vomiting</td>
<td>Two months history of severe protein-losing nephropathy. Progressive weight loss, anorexia and finally vomiting</td>
</tr>
<tr>
<td>Cat 2 DSH, NM, 18m</td>
<td></td>
<td>Poor body condition, 5-7% dehydrated, pale mucous membranes, enlargement of all paws and footpads, firm and painful ulcerated nodules on the ventral aspect of paws</td>
<td>Poor body condition, unable to maintain a standing position, pale mucous membranes, painful footpads, firm ulcerated interdigital and footpads nodules</td>
<td>Poor body condition, hypothermic, severely dehydrated (10-12% estimated), pale mucous membrane, several hard nodules in interdigital spaces of all paws</td>
<td>Poor body condition, bilateral symmetrical nephromegaly, small (up to 5 mm) white nodules in multiple footpads</td>
</tr>
<tr>
<td>Cat 3 DSH, NM, 7y</td>
<td></td>
<td></td>
<td>Poor body condition, 5-7% dehydrated, pale mucous membranes, firm ulcerated nodules in interdigital spaces and footpads of all paws</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat 4 DSH, FS, 5y</td>
<td></td>
<td></td>
<td>Poor body condition, bilateral symmetrical nephromegaly, small (up to 5 mm) white nodules in multiple footpads</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cat 5 DSH, FS, 3y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Euthanased after 4 months</th>
<th>Slight improvement of paw disease after 4 weeks. Euthanized after 4 months</th>
<th>Euthanased after 2 weeks</th>
<th>Unchanged after 3 months</th>
<th>Euthanased after 2 months</th>
</tr>
</thead>
</table>

12 W Bertazzolo et al
<table>
<thead>
<tr>
<th>Signalement</th>
<th>Cat 1</th>
<th>Cat 2</th>
<th>Cat 3</th>
<th>Cat 4</th>
<th>Cat 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLH, FS, 13y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSH, NM, 18m</td>
<td>27.3</td>
<td>18.3</td>
<td>18.0</td>
<td>15.1</td>
<td>27.9</td>
</tr>
<tr>
<td>DSH, NM, 7y</td>
<td>5.98</td>
<td>3.4</td>
<td>3.8</td>
<td>2.6</td>
<td>5.0</td>
</tr>
<tr>
<td>DSH, FS, 5y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSH, FS, 3y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant laboratory results

- **PCV (RR 30–45%)**: 27.3, 18.3, 18.0, 15.1, 27.9
- **RBC×10^{12}/l (RR 5.0–10.0)**: 5.98, 3.4, 3.8, 2.6, 5.0
- **Urea (RR 5–11 mmol/l)**: 29.9, 31.3, 83.7, 32.3, 55.8
- **Creatinine (RR 30–130 μmol/l)**: 194.5, 221, 459.7, 283, 654.2
- **Phosphorus (RR 0.5–1.6 mmol/l)**: 2.6, 2.3, 3.6, 4.1, 9.4
- **Calcium (RR 2.0–2.75 mmol/l)**: 3.4, 2.6, 2.7, 2.1, 1.5
- **Solubility product* [calcium×phosphorus (RR<70)]**: 111.5, 72.4, 119.8, 104, 178.7
- **PTH (pmol/l)**: 19.6 (RR 0.1–5.0), NP, NP, 7.1 (RR 0.1–1.5), 1.1 (RR 0.1–1.5)

**Urinalysis (relevant findings)**

- **USG**: 1.026 (RR 1.035–1.060), 1.025 (RR 1.035–1.060), NP, USG 1.015 (RR 1.035–1.060), USG 1.019 (RR 1.035–1.060)
- **Persistent +3 proteinuria on urine dipstick (Combur Test, Roche)†**: Persistent +3 proteinuria on urine dipstick (Combur Test, Roche)

**Notes**

- DSH, domestic shorthaired cat; DLH, domestic longhaired cat; SF, spayed female; NM, neutered male; y, years; m, months; RR, reference range; USG, urine specific gravity; NP, not performed.
- *Product is calculated with calcium and phosphorus concentration expressed in mg/dl.
- †+3 protein $>$5 g/l.
with larger fragments of glassy refractile material that failed to take up any stain (Fig 2). This was consistent with calcium salts deposits. Rare inflammatory cells (neutrophils, macrophages and spindle cells) were found in some smears. Extracellular bacteria (coccic and rods) were observed in smears obtained by imprint. Occasional giant multinucleated cells were found in samples from cat 4. Cytological findings were suggestive of cutaneous calcinosis in all cases. Cats 3, 4 and 5 also had cutaneous histopathology of paws performed on biopsy material or after necropsy. On histology, multiple spherical loculi demarcated by a fibrous stroma were seen. These loculi contained an amorphous, granular basophilic, von Kossa-positive material. Fibrous stroma sometimes contained lymphoid, epithelioid and occasional multinucleated cells. These findings were consistent with a histological diagnosis of calcinosis circumscripta.

Complete blood count and serum biochemistry were performed on all cats, while urinalysis was performed on cats 1, 2, 4 and 5. Significant laboratory findings are reported in Table 1. All cats had laboratory results suggestive of chronic renal failure (CRF). In cat 5 renal failure was associated with a PLN. All cats had anaemia, azotaemia and hyperphosphataemia. In all cases the solubility product \([\text{calcium} \times \text{phosphorus}] \) \(\text{SP(Ca}\times\text{P})\) was above 70. Cat 5 had also persistent mild hypoalbuminaemia, ranging from 19 g/l to 23 g/l on several evaluations (normal range 25–40 g/l). Urinalysis (evaluated by commercial dipstick, see Table 1) showed evidence of significant proteinuria in only one cat (cat 5), and urine sediment was unremarkable in all four cases examined. Serum parathyroid hormone (PTH) level was determined in cats 1, 4 and 5: it was above the reference range in cats 1 and 4, and in the normal range in cat 5. Results of testing for feline immunodeficiency virus and
Feline leukaemia virus were available for cats 4 and 5 and they were negative.

Lateral and dorsopalmar radiographs of front feet were performed on cat 4: diffused soft tissue mineralization of footpads and interdigital space was evident. Thoraco-abdominal radiographs were performed on cats 4 and 5 and they showed soft tissue mineralization in thoracic and abdominal aorta and in the gastric wall (only cat 4). An irregular, 1.5 to 3 cm subcutaneous inter-scapular area of calcification was palpable and radiographically evident in both cats 4 and 5. In cat 4, a fine needle aspiration of this area revealed the same acellular material observed in cytological smears from paws. In cat 5, this lesion was examined only by postmortem histopathology and consisted of multifocal to coalescing areas of calcification with necrosis of subcutis and muscular layers.

Cats were treated with a combination of intravenous (IV) and subcutaneous (SQ) crystalloids fluids such as 0.9% saline solution or lactated Ringer’s solution (cats 1, 3, 4 and 5), ranitidine (Randil; Menarini) 2 mg/kg/12 h IV, SQ or orally (cats 3, 4 and 5), aluminium hydroxide (Diplogel; Formenti) 10 mg/kg/8 h orally (cat 3), prednisone (Predsolan; Schering-Plough) 2 mg/kg/24 h SQ (cat 5), and benazepril (Fortekor; Ciba-Geigy) 0.5 mg/kg/24 h orally (cat 5). In all cases, a low phosphorus/low protein diet was prescribed. However, food intake was considered unsatisfactory in all cats. A moderate improvement in paw disease was noted only in cat 2 four weeks after presentation: nodules were reduced in size and lameness was less evident. In the other cats, the lesions remain unchanged. Owners requested euthanasia in all cases but four, from two weeks to four months after initial presentation. At the time of writing (three months after diagnosis) cat 4 is still alive. Necropsy could be performed only in case 5. Confluent plaques of calcification of the tunica media of the aorta and other main arteries, end-stage kidney with multifocal tubular calcification, alveolar emphysema with diffuse calcification of arteries and capillaries and mild multifocal hepatic necrosis with subacute to chronic inflammatory infiltration were the relevant findings.

In the cat, paws and footpads diseases can be caused by localised or systemic disorders and local or metastatic neoplasm. Reported causes in

Fig 2. Photomicrograph of a smear obtained by fine needle aspiration biopsy from an interdigital nodule in a cat with paw calcifications. A large amount of amorphous granular, dark-grey to bluish particulate material is evident, along with larger fragments of glassy refractile material that failed to take up any stain. This is suggestive of calcium salts deposits (400×. Hemacolor® stain, Merck; bar equal to 50 μm).
literature are: inflammatory or immune-mediated diseases (microbial, fungal or immune-mediated pododermatitis; plasmacellular pododermatitis; allergic pododermatoses; eosinophilic granuloma complex; uremic vasculitis; ‘drug eruption’; parasitic pododermatoses), irritant contact pododermatitis, endocrinopathies (hypothyroidism, Cushing’s syndrome, diabetes mellitus) and neoplasm: primary (papillomas, squamous cell carcinoma, tricoepithelioma, fibrosarcoma, fibrous malignant histiocytoma) or metastatic (e.g. from lung carcinoma) (Gauguère et al 1992). This paper shows that cutaneous calcinosis of paws should also be considered as an additional differential diagnosis.

Cutaneous calcifications can be classified as dystrophic, metastatic, iatrogenic or idiopathic (Walsh & Fairley 1995, Jackson & Barber 1998, Schaer et al 2001). Dystrophic calcification occurs as a result of local tissue damage (Walsh & Fairley 1995). In dogs and cats, this can occur in foreign body granulomas, interdigital pyoderma, demodicosis, follicular cysts, pilomatrixomas, hyperadrenocorticism and diabetes mellitus (Scott et al 1995, Schaer et al 2001). Metastatic calcifications are associated with disorders of calcium and phosphorus homeostasis leading to a SP(CaXP) greater than 70 (Walsh & Fairley 1995, Jackson & Barber 1998, Schaer et al 2001). Blood vessels, lung, gastric mucosa, kidneys, cutaneous and subcutaneous tissues may be involved (Schaer et al 2001). Any disorders that cause hypercalcaemia and/or hyperphosphataemia (hypervitaminosis D, lymphomas, multiple myeloma, carcinomas, renal diseases, systemic blastomycosis) can be responsible for metastatic calcification (Schaer et al 2001). Iatrogenic calcinosis cutis has been described as a result of percutaneous injection of calcium containing drug (calcium gluconate) in one dog (Schaer et al 2001) and one cat (Ruopp 2001). If no cause can be determined, cutaneous calcification is considered idiopathic (Walsh & Fairley 1995, Jackson & Barber 1998).

In our series, all cats had moderate to severe renal failure, high SP(CaXP) and cutaneous calcification involving only the paws. The association between paw mineralization and renal failure, found in our study, agree with previous reported cases of footpads calcification in seven dogs (Cordy 1967, Legendre & Dade 1974, Kowaliewich & Hawkins 1992, Gross 1997) and in two cats (Bohmer et al 1991, Jackson & Barber 1998). In fact, calcinosis of footpads has been reported only once in a dog not affected by CRF (Stampley & Bellah 1990). Our findings suggest a metastatic pathogenesis for paw mineralisation, possibly supported by a traumatic dystrophic effect on the feet that could occur during stance and gait, as suggested by Jackson & Barber (1998).

In the case reported by Jackson & Barber (1998), paw calcifications regressed three months after the cat had been put on a low phosphorus/low protein diet (Feline Low Protein Diet; Waltham), and SP(CaXP), phosphataemia and PTH level decreased significantly. Four out of the five cats described in our report had, however, a poor prognosis. This could be explained by insufficient intake of specific diets (all cats) and by an advanced stage of the renal disease (cats 3 and 5).

Serum calcium was normal in cat 2, 3 and 4, and low in cat 5. Soft tissue calcifications can also occur with low-normal serum calcium, if phosphataemia is high enough to lead to an elevated SP(CaXP), as in the cases reported by Legendre & Dade (1974) and by Bohmer et al (1991).

Subcutaneous calcification in the interscapular space observed in cats 4 and 5, could reflect a phenomenon termed calciphylaxis in humans (Walsh & Fairley 1995, Essary & Wick 2000). This condition is a kind of metastatic calcification that can be found also with a SP(CaXP) less than 70 (Walsh & Fairley 1995). Calciphylaxis can occur after exposing a patient to a sensitising agent (e.g., PTH, vitamin D, high calcium-phosphate product) and then administering topical or systemic products (e.g., metallic salts, egg albumin, corticosteroids) (Walsh & Fairley 1995). The subcutaneous interscapular area was used for parenteral drug administration in both cats 4 and 5.

Calcinosis was diagnosed by cytology alone in cats 1 and 2 and by both cytology and histopathology in cats 3, 4 and 5. The presence of refractile, granular, basophilic or colourless, heterogeneous material as depicted in Fig 2, is considered cytologically diagnostic for calcium
deposits in human medicine. (Solans et al 1997, Gupta et al 1998, Deshpande & Munshi 1999). Differential diagnosis of abundant calcium mineral in fine needle aspiration biopsy samples includes calcifications associated with neoplasm, granulomatous infection and calcinosis circumscripta. The absence of suspected neoplastic and chronic inflammatory cells on cytopathology, along with appropriate clinical setting, support the diagnosis of calcinosis secondary to CRF and RHPTH in humans (Solans et al 1997, Gupta et al 1998, Deshpande & Munshi 1999). In some smears (in particular from cat 4), mixed inflammatory cells were present (neutrophils, macrophages, spindle cells and multinucleated giant cells). Histopathology of cats 3, 4 and 5 showed that calcium deposits were surrounded by a foreign body reaction. Therefore, mixed inflammatory cells were not unexpected in cytological samples.

**Aknowledgements**
The authors thank Dr Luca Magnoni and Dr Mariella Ferla for referring case 4 and for their assistance.

**References**