

PATHOLOGY

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Calcinosis Circumscripta in the Dog: A Retrospective Pathological Study

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Summary

Calcinosis circumscripta is an uncommon syndrome of ectopic idiopathic, dystrophic, metastatic or iatrogenic mineralization characterized by deposition of calcium salts in soft tissues. This paper is a retrospective study of 77 canine cases. The age of dogs in the study varied from 4 months to 15 years and 55% were < 1 year old, 74% < 2 years old and 88% < 4 years old. Several pure and mixed, typically large breed dogs were affected so that 28.6, 13 and 9% were German Shepherd, Rottweiler and Labrador Retriever respectively. The size of lesions varied from 2 mm to 13 cm in diameter but most lesions were between 0.5 cm and 3 cm in diameter. Lesions were solitary in 82% of the affected dogs, and occurred most commonly on the hind feet (50%) and tongue (23%). With multiple lesions there was no apparent body symmetry. Microscopically, most lesions were well-defined single or multiple variably sized aggregates of amorphous to granular, lightly to darkly basophilic material with or without peripheral granulomatous reaction and surrounded by varying amounts of fibrous connective tissue. Additionally, three small nodular masses in the wall of the jejunum of a dog were diagnosed as calcinosis circumscripta. This is the first reported case of idiopathic intestinal calcinosis circumscripta in the dog.

Introduction

Calcinosis circumscripta is an uncommon syndrome of ectopic mineralization characterized by deposition of calcium salts in soft tissues. These calcium salts consist primarily of hydroxyapatite crystals or amorphous calcium phosphate (Palmer, 1993). It has been reported in many species including human beings, monkeys, dogs, cats, horses, cows, a buffalo, a rabbit and a captive sitatunga (Thompson et al., 1959; Cotchin, 1960; Henderson and Giddens, 1970; Ikede, 1979; Carrara et al., 1982; Line et al., 1984; Anderson and Scott, 1987, 1988; Anderson et al., 1988; Stone et al., 1990; Beroccal et al., 1992; Gross, 1997; Mooney and Glazier, 1997; Yani et al., 2001).

In the literature other synonyms such as tumoral calcinosis, calcinosis cutis, calcium gout, lipocalcinosis, tumoral lipocalcinosis, canine gout, apocrine cystic calcinosis, hip stone,

granulomatosis and kalkgicht have been used to describe this syndrome (Ginel et al., 1992; Palmer, 1993).

Mineralization of soft tissues has been classified into three types according to underlying factors: metastatic, dystrophic and idiopathic calcinosis (Black and Kanat, 1985; Smack et al., 1996).

In human patients, tumoral calcinosis is most frequently metastatic (Smack et al., 1996) but in small animals, in contrast with man, the dystrophic and idiopathic forms occur more frequently than the metastatic form (Palmer, 1993; Ettinger and Feldman, 2000). The syndrome is seen most commonly in young, large breed dogs, with German Shepherd dogs being predisposed (Palmer, 1993). There is only one retrospective study of canine calcinosis circumscripta in the literature (Scott and Buerger, 1988) and other papers in this context have been case reports. In this paper, in addition to study of pathological lesions of 77 affected cases, the first case of intestinal calcinosis circumscripta is reported.

Materials and Methods

This study was conducted on 77 cases of canine calcinosis circumscripta that were diagnosed from 1991 to 2001 in the Department of Pathology and Microbiology at the Atlantic Veterinary College. In this survey, the factors analysed included signalment (including age, sex, breed), affected sites, gross lesions (including size, consistency and morphological pattern), and any history of previous or concurrent illness, trauma or surgery. Additionally, the histopathological characteristics of all cases were reexamined and the gross and microscopic lesions were compared and placed into three categories including early, intermediate and late lesions (Scott and Buerger, 1988).

Results

Age

The age of affected dogs varied from 4 months to 15 years. Forty-two dogs (55%) were < 1 year old, 57 (74%) were < 2 years old and 68 (88%) were < 4 years old.

Sex

Of the 77 affected cases, 41 (53%) were male and 36 (47%) were female.

Breed

The 77 cases of calcinosis circumscripta were seen in several pure and mixed breeds of dogs including German Shepherd (22 cases), Rottweiler (10 cases), Labrador (seven cases), Great Dane (three cases), Golden Retriever (three cases), Boxer (three cases), Siberian Husky (two cases), Saint Bernard (two cases), Shih Tzu (two cases), Irish Wolf hound (two cases), Poodle (two cases) and one each of Greyhound, Doberman Pincher, Jack Russell terrier, Bouvier, West Highland White terrier, Airedale terrier, Belgian sheepdog, and English springer spaniel. As a result 28.6, 13 and 9% were German Shepherd, Rottweiler and Labrador Retriever dog breeds respectively. Additionally, about 14% (11 cases) of the dogs were mixed breed dogs, derived from large breeds such as German Shepherd, Rottweiler, Labrador and Doberman.

Affected sites

The locations of the gross lesions in the present study were in the subcutaneous tissue of different parts of the body, oral cavity and in one case small intestine. Of the 77 cases studied, 21 (27%), 18 (23%) and 18 (23%) were seen on right hind foot, left hind foot and tongue respectively. The metatarsal area (eight cases), metacarpal area (five), tarsus (six), elbow (five), hock (five) and scapula (five) were the most common sites of occurrence on the limbs. Moreover, in 18 cases with lingual lesions, nine were on the dorsal surface, six were on the ventral surface and three were on the base or frenulum of the tongue. Other locations included subcutaneous tissue of lip (two cases), gingiva (two), pinnae (three), right side of transverse process of cervical vertebrae (C3–C4) (two), mandible (one), subcutaneous and deep muscular tissue of right femur (two), subcutaneous tissue of right ischium (one), subcutaneous tissue of medial side of right stifle (two), subcutaneous tissue of paw (one), subcutaneous tissue of interdigital area (one), tendon of supraspinatus muscle (one), right shoulder (two), phalangeal area (one), subcutaneous tissue of neck (one), subcutaneous tissue of left side of thorax (one), subcutaneous tissue of back (one) and jejunum (one).

Previous history or concurrent illness

Prior or concurrent illness was reported in 11 cases. Concurrent existence of melanoma and basal cell epithelioma in the muzzle of a 15-year-old German Shepherd dog, cutaneous histiocytoma on the head of a Rottweiler dog, multiple exostosis and osteochondritis dissecans (OCD) of the left shoulder of an 8-month-old Irish wolf hound (with calcinosis lesion in the right elbow) appeared unrelated to calcinosis circumscripta. In other cases, concurrent lesions could relate to the calcinosis circumscripta; for example, there was a history of stick chewing in two dogs with lingual lesions, prior ear cropping at the site of lesions in a 1-year-old Boxer, chronic lameness for 2 years and acute signs for 2 months in a tendon of supraspinatus muscle in a 5-year-old Rottweiler, history of fracture and surgery in two dogs at the location of occurrence

of lesions and history of OCD and chronic proliferative synovitis in the medial aspect of the left tarsus of a 9-month-old Rottweiler with calcinosis of joint capsules.

Gross lesions

The size of lesions varied from 2 to 13 cm in diameter. Most lesions were between 0.5 and 3 cm in diameter. Lesions were solitary in 63 cases (82%), multiple in 14 cases (18%) and with multiple lesions there was no apparent symmetry. Gross lesions varied from a small, firm, white nodule (2 mm) to a large round cystic mass (13 × 9 cm) containing more than 1 l of chalky white material. Some lesions were freely movable while others were tightly adherent to the surrounding tissue. For example, a 4-month-old Golden Retriever dog had an approximately 5 × 3 cm mass below the gum in left maxillary region, posterior to the canine tooth which extended into the nasal turbinates, dislodging the incisor teeth and inducing chronic gingivitis. The cut surfaces of most lesions had multifocal nodules contain gritty chalky white material.

Histopathological lesions

Microscopically, all the lesions were seen as well defined single or multiple cystic-like structures containing amorphous to granular, lightly to darkly basophilic materials with or without peripheral granulomatous reaction and surrounded by a varying amounts of fibrous connective tissue. The histopathological lesions were placed into three categories, as correlated to age of the lesion.

Stage I (early lesions)

Six cases (8%) were characterized by round to irregular shaped, variably sized deposits of amorphous to granular basophilic material found freely in normal tissue or surrounded by a thin layer of connective tissue with minimal or without inflammatory reaction.

Stage II (intermediate lesions)

Thirty-one cases (40%) were characterized by round to irregular shaped variably sized deposits of amorphous to granular basophilic material surrounded by mild to moderate granulomatous reaction, epithelioid macrophages admixed with fewer small to large multinucleated giant cells (from two to >40 nuclei), occasional lymphocytes, plasma cells and neutrophils and associated with variable amounts of fibroplasia.

Stage III (late lesions)

Forty cases (52%) were characterized by round to irregular shaped, variably sized deposits of amorphous to granular basophilic material surrounded by prominent granulomatous reaction, inflammatory mononuclear cells and thick layers of fibrous connective tissue. In four cases (5%), osseous and chondroid metaplasia was associated with the lesions.

With regard to gross consistency, early and intermediate lesions usually were fluctuant or cystic and late lesions were firm.

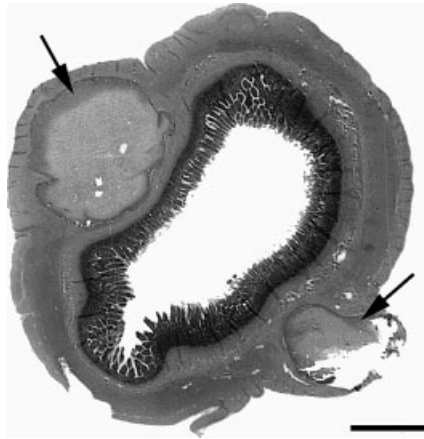


Fig. 1. Dog: calcinosis circumscripta in the jejunum. Note the two expansile aggregates of amorphous mineralized material (arrows) within the muscular layer of the jejunal wall. Haematoxylin and eosin stain; bar = 2 mm.

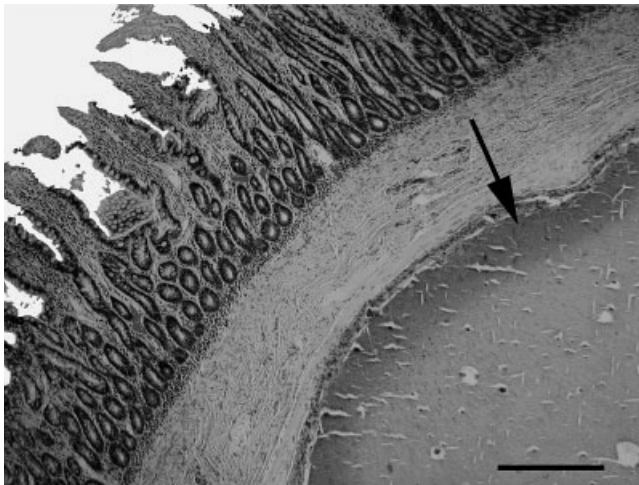


Fig. 2. Dog: Calcinosis circumscripta in the jejunum. Higher magnification of Fig. 1, showing mineralized aggregate (arrow) surrounded by thin layer of granulomatous inflammation. Haematoxylin and eosin stain; bar = 400 μ m.

In the present study, three small nodular masses, about 0.3–4 mm in diameter within the wall of jejunum of a 9-year-old Belgian sheep dog were diagnosed as calcinosis circumscripta (Fig. 1). There was no previous history of surgery but the animal had been vomiting for 10 days. Histopathological examination of these lesions showed relatively large, well defined, deposits of lightly basophilic material (mineralization) surrounded by a thin layer of epithelioid macrophages with occasional multinucleated giant cells and connective tissue within the muscular layer of jejunum (Fig. 2). Additionally, there was a mild increase in the numbers of lymphocytes, plasma cells and eosinophils within the lamina propria and at the base of crypts and diffuse moderate increase in collagenous connective tissue in the submucosa.

Discussion

In this study the ages of dogs ranged from 4 months to 15 years, but 74% of the affected dogs were <2 years and

88% were <4 years of age. This is in agreement with the veterinary literature, which reports calcinosis circumscripta occurring in dogs of all ages but is most commonly found in younger dogs, particularly <2 years of age (Ellison and Norrdin, 1980; Scott and Buerger, 1988; Gross et al., 1992; Palmer, 1993). Furthermore, consistent with other reports, no sex predilection was apparent in this study. Most of the affected dogs were large breeds; 27% German Shepherds, 13% Rottweilers and 9% Labrador Retrievers. Although these data are in agreement with other literature, the affected rate of German Shepherd is less than those reported in the literature (Scott and Buerger, 1988; Palmer, 1993). This study also suggests that Rottweilers and Labrador Retrievers are at an increased risk.

Of the 77 dogs in the present study, 39% had lesions on the right or left feet and 18% had lesions on tongue. These data are consistent with previous studies but the rate of tongue involvement is higher. The genesis of lingual lesions in dogs is obscure but it is possible that repetitive tissue injury or heterotopic salivary gland degeneration provides a focus for dystrophic mineral deposition (Palmer, 1993; Movassaghi, 1999). In the present study there was a history of wood or stick chewing in two of the dogs with lingual lesions.

In general, there was no apparent predilection for age, sex or which side of the body or tongue would be affected. One apparent relationship between breed and lesion site was observed in this study. Of the three Boxer dogs in this study, two had lesions in the pinnae, one of them being at the site of prior ear cropping. It is suggested that Boxer dogs are prone to ear pinnae lesions especially at the site of prior ear cropping (Gross et al., 1992).

Histopathological lesions of calcinosis circumscripta can be placed into three categories which appear to reflect lesion age and gross consistency, but this has been controversial. The categorization of histological lesions in this study is in agreement with results of Scott and Buerger (1988). However, it appears this categorization system has little clinical importance since all lesions are cured by complete surgical removal without recurrence.

The pathogenesis of this syndrome is not completely understood and a variety of factors exist which allow different clinical scenarios to occur. In general, the disorder may be classified into four major types according to the type of calcification process and aetiology.

Dystrophic

This type occurs in the setting of normal serum calcium and phosphate levels and the calcification is localized to a specific area of tissue damage. The primary lesion can be due to injury, necrosis, inflammation or neoplasia. Tissue damage may be due to mechanical, chemical, infectious or other factors. Cases of calcinosis circumscripta following severe chronic inflammation such as a reaction to a foreign body, otitis externa, interdigital pyoderma, demodicosis, neoplasia and apocrine gland degeneration have been reported (Christie and Jabara, 1964; Pool et al., 1972; Legendre and Dade, 1974; Gross et al., 1992). In five of the 77 cases from this study there was a clinical history of prior repetitive trauma at the site of lesions. This supports the hypothesis that trauma can be a predisposing factor for the development of calcinosis circumscripta. However the authors found no supporting evidence for the sweat

gland vulnerability as an etiological factor. This is in agreement with the findings of Scott and Buerger (1988).

Metastatic

This type occurs mostly in human beings, in the setting of abnormal calcium or phosphate metabolism and generally is associated with hypercalcaemia and/or hyperphosphataemia such as chronic renal failure or end stage kidney disease and vitamin D toxicosis. A few reports in the veterinary literature, describe calcinosis circumscripta in association with renal failure (Cotchin, 1960; Cordy, 1967; Legendre and Dade, 1974; Croom and Houston, 1994; Gross, 1997; Jackson and Barber, 1998). In the dogs and cats with renal failure, a common presenting lesion has been calcification of foot pads, but widespread visceral and vasculature mineralization is also reported (Cordy, 1967; Legendre and Dade, 1974). It is not known why metastatic calcification due to chronic renal failure affects the footpads primarily in dogs and cats. In human beings, the most common locations of metastatic calcification are around large joints such as knees, elbows and shoulders, in a symmetrical distribution. In all reported dogs, the renal disease was lethal and no treatment was attempted to resolve the ectopic mineralization. The lesions in one cat with renal hyperparathyroidism recurred after surgical resection but responded to dietary phosphorus restriction (Jackson and Barber, 1998). None of the dogs in this study had previous or concurrent renal failure. This finding is consistent with observations of other investigators that the lesions usually occur without renal disease (Scott and Buerger, 1988; Palmer, 1993).

Idiopathic

This type occurs in the absence of known tissue injury or systemic metabolic defect. No causative factor is identifiable. Breed and familial predilection can occur; specifically in human beings, calcinosis circumscripta can be inherited as an autosomal recessive trait. In dogs, hereditary predilection has been suggested by the occasional occurrence in related dogs (Seawright and Grono, 1961; Owen, 1967; Flo and Tvedten, 1975). Moreover, several cases of paravertebral calcinosis circumscripta, especially in the cervical spine, have been reported without any underlying problem in both dogs and human beings (Lewis and Kelly, 1990; Marks et al., 1991; McEwan et al., 1992; Kokubun et al., 1996). In the present study, two German Shepherd dogs each had approximately 3 cm diameter masses on right side of cervical vertebrae (C3–C4) without any underlying disease. A syndrome of calcium phosphate or hydroxylapatite deposition has been reported in young puppies of some breeds, especially Great Danes (Woodard et al., 1982; Marks et al., 1991; Palmer, 1993; Short and Jardine, 1993; Wunschmann et al., 2000). These cases showed signs of paraplegia, incoordination, pathologic spondylolisthesis and mineral deposition within vertebral canal and seem distinct from the paravertebral lesions seen in this study. The early onset of disease and equal sex distribution suggested a congenital or hereditary malformation (Flo and Tvedten, 1975; Woodard et al., 1982; Palmer, 1993; Wunschmann et al., 2000). A hereditary form of the human disease, characterized by early onset and higher familial incidence has been reported to be linked to a point mutation in the type II procollagen

gene (Basualo et al., 1993). In this study, none of dogs had previous or concurrent clinical signs of this syndrome. The existence of multiple exostoses and osteochondritis dissecans (OCD) of the left shoulder with a calcinosis lesion in the right elbow of a dog appeared unrelated to mentioned syndrome. But, diagnosis of OCD and chronic proliferative synovitis in the medial aspect of left tarsus of a 9-month-old Rottweiler with calcinosis of joint capsules could be a form of this syndrome. Mitogenic effects of calcium pyrophosphate dehydrate and hydroxylapatite on canine synovial cells has been reported (Cheung et al., 1984).

Iatrogenic

This type arises secondary to a treatment or surgical procedure with calcification typically occurring at the invasive site and can also be classified as dystrophic calcification. In some cases, calcinosis circumscripta has been reported in association with medroxyprogesterone and proligestone injections, polydioxanone suture material and previous surgical procedures (Kirby et al., 1989; Ginel et al., 1992, 1995; Ferguson, 1996; Davidson et al., 1998; O'Brien and Wilkie, 2001). In the present study, only two of 77 cases had previous history of fracture and surgery at the site of lesion occurrence.

This study reviews 77 cases of calcinosis circumscripta describing several relationships to signalment, affected sites, gross and histopathological lesions or concurrent disorders. The results of this study show that a variety of predisposing factors such as repetitive trauma and injury can play a role in inducing this syndrome in apparently healthy dogs. None of the dogs in this study had underlying metabolic disease and complete surgical resection of the lesions was curative in all cases. Additionally, we report the first case of idiopathic intestinal calcinosis circumscripta in the dog. It is hoped that further studies will better define the underlying causes of calcinosis circumscripta in the dog.

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