CASE REPORT

Idiopathic sterile pyogranuloma in three domestic cats

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Pyogranulomatous inflammation has been extensively described in cats, in particular in cases of feline infectious peritonitis and also associated with Mycobacteria, Actinomyces, Nocardia, Rhodococcus and fungal infections. Idiopathic sterile pyogranulomatous dermatitis has also been described. In this case series we describe the clinical presentation, histopathology and outcome of three cases of feline idiopathic sterile steroid-responsive pyogranuloma with different presentation and different locations of the lesion, but with the common feature of having a mass with no superficial skin involvement.

Journal of Small Animal Practice (2020) **61**, 202–205
DOI: 10.1111/jsap.12853

Accepted: 2 March 2018; Published online: 15 May 2018

INTRODUCTION

Pyogranulomatous inflammation (PI) is a chronic inflammatory lesion characterised by a predominance of macrophages and neutrophils, often in combination with plasma cells and giant cells (Raskin 2001). Generalised PI has been extensively described in the veterinary literature, particularly in cases of feline infectious peritonitis (FIP) (Weiss & Scott 1981, Kipar *et al.* 2005). Cutaneous, subcutaneous and, more rarely, systemic PI in cats is mainly associated with mycobacteria and fungal infections (Malik *et al.* 1992, 1994, 2000, Brömel & Sykes 2005, Baral *et al.* 2006) with sporadic implication of Actinomyces, Nocardia, Rhodococcus, Streptomyces, Francisella, Bartonella and Leishmania (Patel 2002; Valentine *et al.* 2004; Malik *et al.* 2006; Farias *et al.*, 2007; Santero *et al.* 2008; Sharman *et al.* 2009; Varanat *et al.* 2012;Traslavina *et al.* 2015). Idiopathic sterile pyogranulomatous dermatitis has also been described in cats (Scott *et al.* 1990). We describe the clinical presentation and outcome of three cases of feline idiopathic sterile pyogranuloma with different presentation and locations, but with the common picture of a mass with no superficial skin involvement. To our knowledge sterile pyogranuloma with mass appearance and absence of skin involvement have not previously been described in cats.

CASE 1

A 5-year-old male neutered domestic short hair (DSH) cat was presented for investigation of a right sided naso-maxillary mass. Generalised gingival inflammation, more severe over the right canine tooth, was noticed at a routine medical check. A dental polish, descale and a right canine root extraction was performed by the referring veterinarian. The facial swelling appeared 2 weeks following the dental procedure and the cat was treated with 6 weeks of amoxicillin-clavulanic acid without improvement. The owner did not report any clinical signs apart from occasional sneezing during the previous few weeks. On physical examination the patient was bright and alert. There was a firm, poorly defined mass extending from the right proximal maxilla to the nasal region causing facial deformation. No ulceration or skin lesions were present; oral examination was unremarkable except for a swelling on the right side of the proximal maxilla, close to the area of previously removed canine tooth. Complete blood count (CBC) and biochemistry were unremarkable, FeLV antigen and FIV antibody tests were negative.

Oral radiography ruled out a remaining canine tooth root. Due to the high suspicion of neoplasia a CT scan of head, neck and thorax was performed. The CT scan confirmed the soft tissue mass on the nasal dorsum extending laterally to the missing canine tooth and associated with lysis of the incisive and nasal bones. The mass extended into the right nasal cavity with destruction of the nasal turbinates and mild deviation of the nasal septum (Fig 1).

Surgical wedge biopsies were taken after incision and blunt dissection of the skin and subcutis. The biopsies were taken from two different sites within the mass to increase the chances of collecting a representative sample and were immediately submitted for histopathology. Due to the high suspicion of neoplasia, tissue samples for culture were not taken and no antibiotics or other types of treatment were started. Microscopic examination exhibited severe pyogranulomatous and lymphocytic cellulitis and mild pyogranulomatous and lymphocytic myositis (Fig. 2a, b).

There was no evidence of neoplasia in any of the samples examined. No infectious etiological agents could be detected following Gram, Ziehl Nielsen (ZN) and Periodic Acid Schiff (PAS) staining. Immunohistochemistry for coronavirus FIPV3-70 anti-feline coronavirus antibodies (Tammer *et al*. 1995) was negative. The sample was sent for pan-fungal (ITS1-ITS2 region of ribosomal DNA) as previously published (Lau *et al*. 2007) and mycobacteria PCR assay (mycobacterial ITS1-ITS2 regions) on the paraffin block sample as previously published (Hughes *et al*. 1997, Fyfe *et al*. 2008) both of which were negative. Bacterial 16s RNA probe FISH analysis for eubacteria was negative (Maunder *et al*. 2016). On clinical examination the mass remained of similar size for the following 2 months but the sneezing became more frequent. Prednisolone treatment was started at 1 mg/kg daily orally and the mass reduced in size and the sneezing markedly improved, the same dose of prednisolone was continued for 12 months until last follow-up. The cat was still alive at the time of writing 12 months after presentation and the facial swelling and the sneezing resolved almost completely.

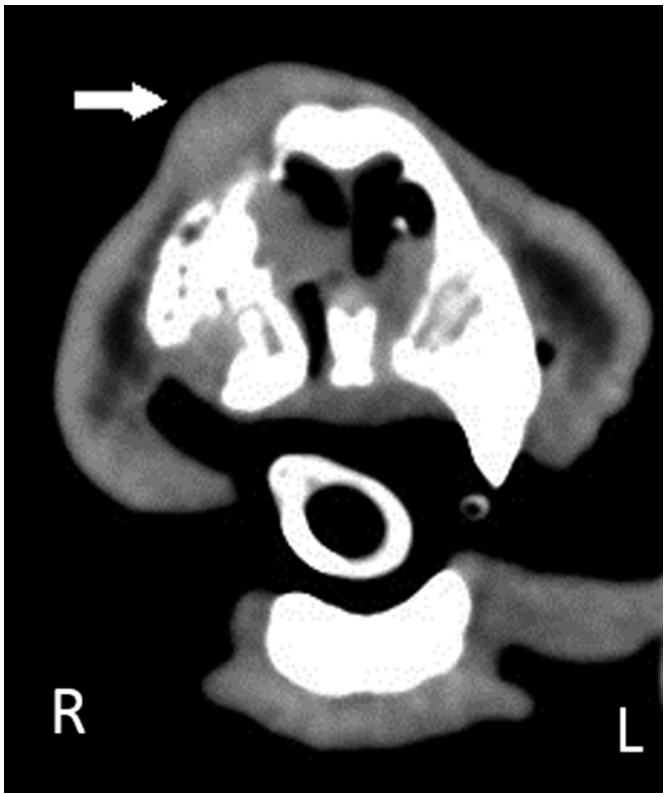

FIG 1. Case 1, 5-year-old male neutered DSH cat. Transverse CT image in bone window of the nasal cavity at the level of the palatine fissures. Dorsal soft tissue density mass on the right side, causing lysis of the incisive and nasal bones and extending into the right nasal cavity without crossing midline

CASE 2

A 6-year-old female neutered outdoor DSH was presented for further investigation of an abdominal mass. The referring veterinary surgeon detected the mass as an incidental finding when the cat presented for annual booster vaccination. The patient did not have any history of previous illness and the owner did not report any current problems or clinical signs; the cat was otherwise fit and well. On abdominal palpation a non-painful, firm, partially mobile mass was present in the mid-caudal abdomen. At this stage, considering the size of the mass in the abdomen and the clinical presentation, the most likely diagnosis was neoplasia although FIP, fungal and mycobacterial granuloma were also considered. CBC and biochemistry were unremarkable apart from mild hyperglobulinaemia 54 g/L (reference interval 24 to 47). FIV antibody and FeLV antigen tests were negative. Abdominal ultrasound showed a heterogeneous mass with mixed echogenicity and no other abnormalities. The mass measured approximately 5×4 cm, and was thought to originate from the

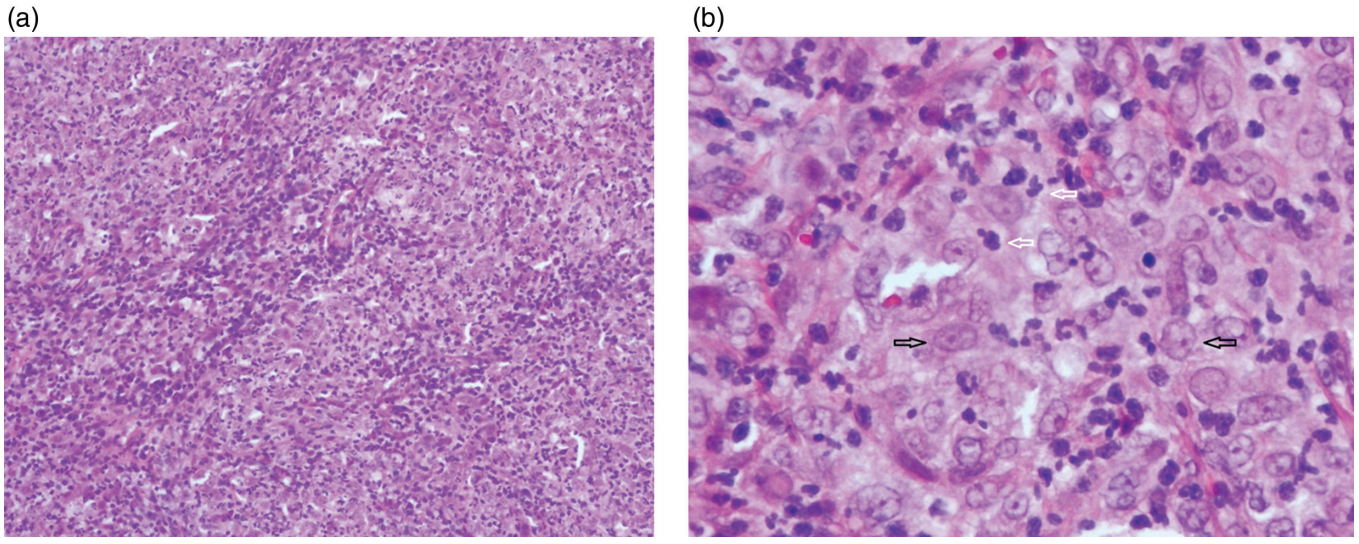

FIG 2. (a,b) Case 1, 5-year old male neutered DSH cat. Biopsy of subcutaneous tissue containing large numbers of macrophages, neutrophils, moderate numbers of lymphocytes and lesser numbers of plasma cells. H&E. stain ×100 on the left and ×400 on the right or Bar = 100 µm. White arrow neutrophils, black arrow macrophagess of plasma cells

mesenteric lymph node. Cytology of fine needle aspirates (FNAs) of liver and spleen taken to rule out the possibility of related disease in those organs was unremarkable. An FNA of the mass revealed PI with mixed, mainly neutrophils and macrophages, infiltrates. An ultrasound-guided Tru-cut biopsy of the mass was obtained under general anaesthesia, which confirmed the lesion to be pyogranulomatous. In view of the continued high suspicion of neoplasia, an exploratory laparotomy was performed. The mass was confirmed to originate from the mesenteric lymph node and could not be resected without damage to the intestinal blood supply. Multiple wedge biopsies were obtained to submit for culture and histopathology. Histopathological examination showed a pyogranulomatous and necrotising lymphadenitis, with fibrosis. No aetiological agents were visible on Gram, ZN and PAS staining. Immunohistochemistry for coronavirus (FIPV3-70 anti-feline coronavirus antibodies) was also negative. The sample was sent for pan-fungal PCR (ITS1-ITS2 region of ribosomal DNA) on paraffin tissue block and mycobacteria PCR (Mycobacterial ITS region) on frozen sample that were both negative. Bacterial 16s RNA probe FISH analysis for eubacteria was negative. Due to the incidental finding and its asymptomatic nature it was decided to monitor the mass and no treatment was given. The mass remained of similar size and no clinical signs related to it were ever reported. The cat was still alive and well almost 2 years after diagnosis when she died in a road traffic accident.

CASE 3

A 6-year-old male neutered DSH was presented for further investigation of a 5 to 6 cm right submandibular subcutaneous mass. The mass was first noticed by the owner 5 months previously when it was approximately 3 cm in diameter; the mass was not painful and there were no associated clinical signs. The patient was treated by the referring veterinarian with a 7-day course of meloxicam and amoxicillin-clavulanic acid with no improvement. On presentation the cat was still clinically well and the owner did not report any problems or clinical signs except for the mass. It was suspected to be neoplastic and thoracic radiography and a wedge biopsy sample were taken under general anaesthesia. Thoracic radiography showed focal mineralisation of the left caudal lung lobe – considered an incidental finding – but was otherwise unremarkable. The histopathological diagnosis was marked pyogranulomatous and lymphocytic cellulitis with mild myositis and no evidence of neoplasia. The mass continued to grow and, neoplasia remained high on the differential list, so the mass was surgically resected. The second histopathology report confirmed the previous diagnosis of a pyogranuloma, and no aetiological agents could be found with PAS, Gram and ZN staining. PCR and culture for Mycobacteria were performed on frozen (stored at –80°C) and fresh tissue, respectively, and were both negative. A pan-fungal PCR (ITS1-ITS2 region of ribosomal DNA) on paraffin block tissue was also negative except for isolation of "*Candida albicans*." Although this was most likely a contaminant, the patient was prescribed a 3-month course of itraconazole. One month later new numerous nodules non-associated with the previous removed mass were found in the lymphatic chain of the neck, together with an enlarged prescapular lymph node, but there was no regrowth of the previous removed granuloma. MRI confirmed the presence of the nodules in the neck and an enlarged right prescapular lymph node; no other abnormalities were found. Radiography of the thorax and abdominal ultrasound were unremarkable. The prescapular lymph node and three nodules in the neck were removed for diagnostic purposes. Histopathology confirmed the presence of pyogranulomatous cellulitis and myositis, with mild dermal fibrosis and pyogranulomatous lymphadenitis. No aetiological agents could be found despite repeated examination using PAS, Gram and ZN stains. Tissue culture, pan-fungal and mycobacteria PCR were again negative. Immunohistochemistry for coronavirus antigen (FIPV3-70 anti-feline coronavirus antibodies) and 16s RNA probe FISH analysis for eubacteria were performed and were both negative. The lesions remained unchanged for the following 3 weeks and a dose of prednisolone 1 mg/kg daily for 2 weeks was prescribed but produced no improvement. The dose was increased to 3 mg/kg for the following 2 weeks, reducing to 2 mg/kg for the following month. Despite the initial lack of response, the lesions markedly improved and completely disappeared over the following 2 months. The prednisolone was gradually reduced and stopped. At the time of writing the cat was still asymptomatic and no recurrence of the lesions has been documented, more than 1 year after initial presentation.

DISCUSSION

To our knowledge this is the first report of feline idiopathic sterile pyogranuloma without skin involvement. The pyogranulomas here described affected young to middle-aged DSH cats, they had varied locations but similar histopathological features, with no aetiological agents found despite extensive investigations. The 16s rRNA PCR for Mycobacteria species in fresh, frozen or even in paraffin-embedded tissue sample is considered a very sensitive and specific test for diagnosis of lepromatosis/mycobacteriosis in cats compared to histopathology and ZN staining, so the possibility of a false negative is unlikely (Hughes *et al.* 2004). The pan-fungal PCR amplification of the ITS1-5·8s-ITS2 region of ribosomal DNA is considered a sensitive test for detection of fungi and, in combination with conventional laboratory tests, it improves the accuracy of fungal detection in tissue specimens (Lau *et al.* 2007), so a fungal infection was considered extremely unlikely. All the formalin-fixed and paraffin-embedded tissue samples for PCR were fixed for a maximum of 24 hours and analysed within 7 days from sample collection, limiting false-negative results as previously published (Hughes *et al.* 2004, Reppas *et al.* 2013). On the 16s RNA probe FISH analysis no bacteria could be found. This test is considered more sensitive than culture in the detection of bacteria, ruling out the possibility of a bacterial involvement. Bartonella is often asymptomatic in cats, although recently Bartonella has been isolated in pyogranulomatous myocarditis in two cats (Varanat *et al.* 2012). Prevalence of Bartonella in cats can be quite high and the association of Bartonella with

the manifestation of any concurrent disease can be difficult to prove (Barnes *et al*. 2000). In our case we did not test for Bartonella, so although unlikely we could not completely rule out this possibility. Furthermore, the lack of significant progression or development of systemic lesions in particular after treatment with prednisolone in cases 1 and 3 was more consistent with a non-infectious process. The clinical response to prednisolone in cases 1 and 3 may, in fact, indicate a possible immune-mediated/inflammatory aetiology, similar to that reported in dogs (Fraga-Manteiga *et al*. 2016) and currently still under investigation (Bexfield *et al*. 2015).

In conclusion we have reported three cases of idiopathic sterile granuloma with mass appearance in cats. The granulomas had an overall slow growth and benign progression, despite the aggressive clinical appearance and the remarkable size of the masses in all cases. In case 3, surgical resection originally controlled the disease, but due to the development of other lesions 1 month later, the benefit of surgery, except for diagnostic purposes, remains uncertain. Immunosuppressive treatment with prednisolone could be beneficial but more studies are required to support this notion.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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