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Case Report

Proliferative arteriopathy of the nasal philtrum in two Brazilian Mastiff dogs

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Abstract

Proliferative arteritis of the canine nasal philtrum is an unusual disease with an unknown etiology and very few cases described in literature to date. Two patients with characteristic lesions underwent biopsy and confirmation by histopathological assessment. The first case was treated with oral prednisolone once daily and topical tacrolimus twice daily. The second case was treated twice daily with pentoxifylline and topical tacrolimus. Both treatments were successfully used by other authors previously. In result, clinical improvement varied among patients. The lesion of the first case showed no clinical improvement after 15 days of treatment. The second case showed a mild improvement of the initial lesion. In conclusion, treatment with tracolimus, pentoxifylline, and prednisonole appears to have a good effect in mild and early lesions. The objective of this paper was to describe the clinical findings, treatment options and histopathological aspects in two Brazilian Mastiff dogs, not previously reported.

Key words: arteritis, artheriopathy, nasal philtrum.

Introduction

Proliferative arteritis is a specific canine disease of the nasal philtrum with an unknown etiology (2). The disease appears to be associated with a primary inflammatory process targeting medium and large arteries of the nasal philtrum with secondary vascular occlusion, local hypoperfusion and necrosis (6).

There are few reports in the literature on, most notably, the Saint Bernard (4, 5, 6, 8), giant Schnauzer (6), Samoyeda (1) and Basset Hound (5) breeds. Clinically, patients show a solitary, well-demarcated and crusted ulcer restricted to the nasal philtrum (2, 6). No age or sex predilections were reported. Differential diagnosis include lupus erythematosus, pemphigus vulgaris, contact hypersensitivity, uveodermatologic syndrome, leishmaniasis, fungal diseases, distemper, trauma and some neoplastic diseases, like epitheliotropic lymphoma (6). Final diagnosis is based upon specific clinical signs and histopathological assessment. Microscopically, there are different degrees of subendothelial proliferation of spindle cells, deposition of extracellular matrix and/or variable inflammation (3).

This study aimed to describe the clinical and pathological features of this disease in two unrelated Brazilian Mastiff dogs. To the best of the author's knowledge, this is the first such report on this breed.

Materials and methods

Case report 1

A 4-year-old, male, Brazilian Mastiff dog was presented to a private veterinary clinic with a two-year history of a painful, linear and crusted ulcer located on the nasal philtrum. The ventral aspect of the ulcer had a "V" shaped configuration (Fig. 1A). No other clinical abnormalities were noted. The dog's owner reported a previous unsuccessful treatment with a topical cream composed of betamethasone, tolnaftate, gentamicin, and

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clioquinol (Quadriderm®; Intervet Shering-Plough; São Paulo; Brazil) twice daily and 30 mg/Kg oral cephalexine (Rilexine®; Virbac; São Paulo; Brazil) twice daily for a period of two months. Due to lack of clinical improvement, two 4 mm punch biopsy samples from the margins of the ulcer were collected and assessed by histopathology. Histopathology revealed serocellular neutrophilic crusts, parakeratotic hyperkeratosis, neutrophilic exocytosis, intracorneal neutrophilic pustules, spongiosis and hydropic degeneration of basal cells (Fig. 2). The superficial dermis presented a lichenoid inflammatory infiltrate composed of plasma cells, lymphocytes and melanin-laden macrophages (Fig. 3). Dermal arterioles displayed a mild to moderate subendothelial spindle cell proliferation and deposition of an extracellular myxoid material (Fig. 4) highlighted in blue with Alcian Blue stain (Fig. 5) which caused varied degrees of luminal obliteration (Fig. 6). No signs of arteritis were found. Immediately after the biopsy procedure, topical rifampicin (Rifocina Spray®; Sanofi; São Paulo; Brazil) twice daily were prescribed in order to reduce secondary bacterial infection, but produced only a very mild clinical improvement. Afterward, the patient was managed with 1 mg/Kg oral prednisolone (Alcort®; Castel Pharma; São Paulo; Brazil) once daily and 0.1% topical tacrolimus (manipulated formula) twice daily for 15 days. At recheck appointment, no improvement was noted. The ulcer is still present as of the date of this report (Fig. 7A).

Case report 2

A 1-year-old, male, Brazilian Mastiff dog was presented to a private veterinary clinic with a linear ulcer located at the nasal philtrum. The ulcer had a "V" shaped format characteristic of this disorder (Fig. 1B). No other clinical abnormalities were noted. Two 4 mm punch biopsy samples were obtained from the margins of the ulcer and submitted to microscopic analysis. Histological examination was the same as described for Case 1. The patient was submitted to 0.1% topical tacrolimus and 5 mg/Kg petoxifylline (Proex® - Cepav Laboratórios; São Paulo; Brazil) twice daily. After 21 days of treatment, the lesion started to worsen. Oral treatment with 1 mg/kg of prednisolone (Alcort®; Castel Pharma; São Paulo; Brazil) once daily for 15 days was prescribed. A mild clinical improvement was achieved; however, the ulcer is still present (Fig. 7B).

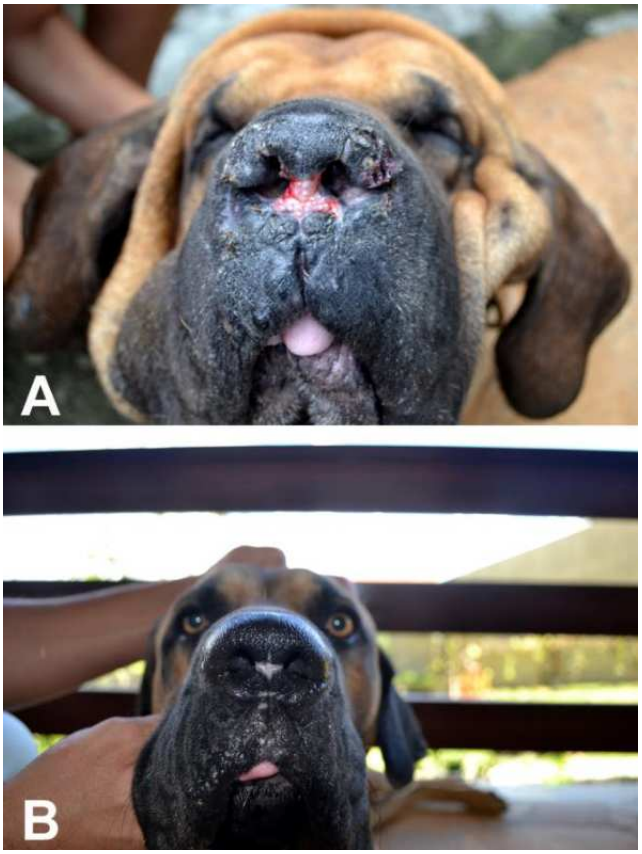


Figure 1. **A.** Case 1. A classical linear ulcer located on the nasal philtrum displaying a "V" shaped configuration on its ventral aspect. **B.** Case 2. A classical linear ulcer located on the nasal philtrum displaying a "V" shaped configuration on its ventral aspect.

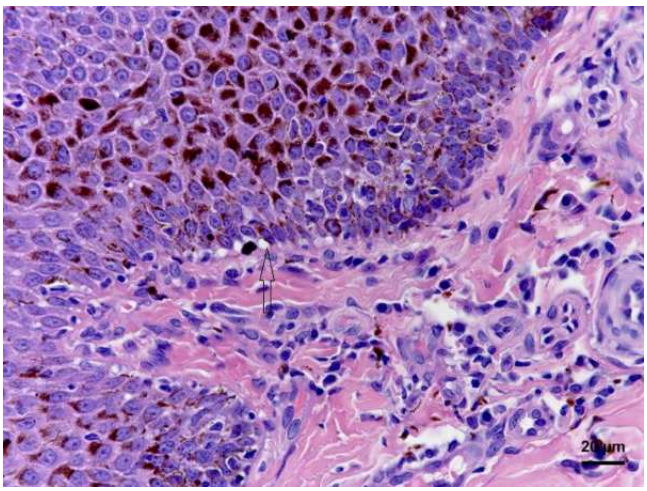


Figure 2. Basal cell hydropic degeneration (arrow), Hematoxylin and eosin, Bar = 20 µm.

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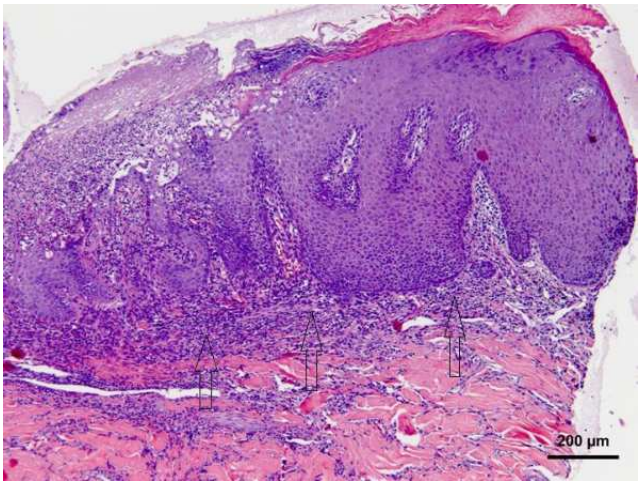


Figure 3. Superficial dermis, lichenoid and band-like inflammatory infiltrate of plasma cells and lymphocytes (arrows), Hematoxylin and eosin, Bar = 200 µm.

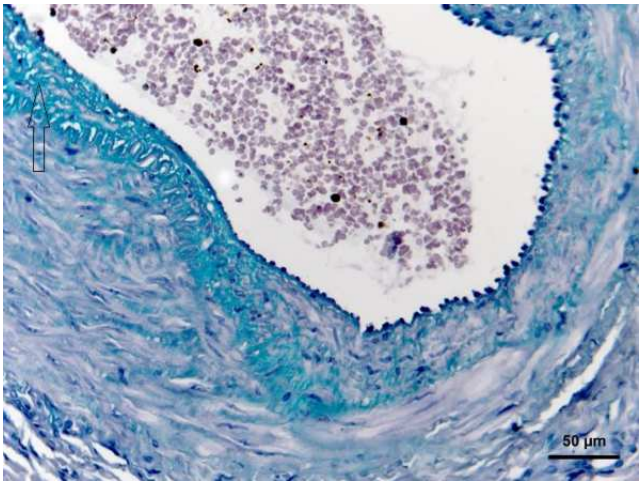


Figure 5. Deep dermis, large arteriole. Subendothelial deposition of an extracellular blue myxoid matrix (arrow), Alcian Blue stain, Bar = 50 µm.

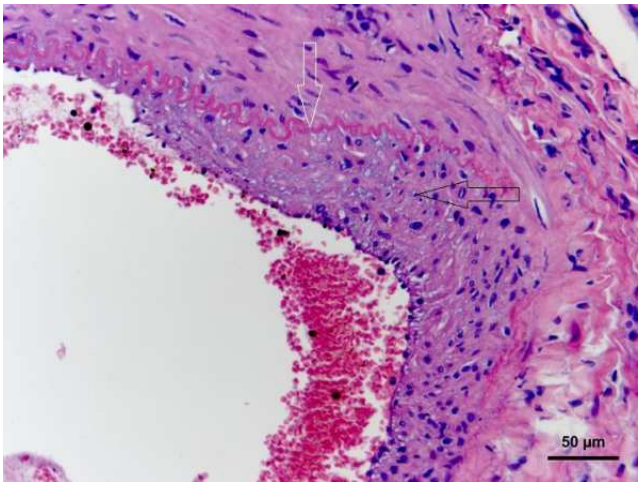


Figure 4. Deep dermis, large arteriole. Subendothelial spindle cell proliferation and deposition of an extracellular basophilic myxoid matrix (black arrow). Internal elastic lamina (white arrow). Hematoxylin and eosin, Bar = 50 µm.

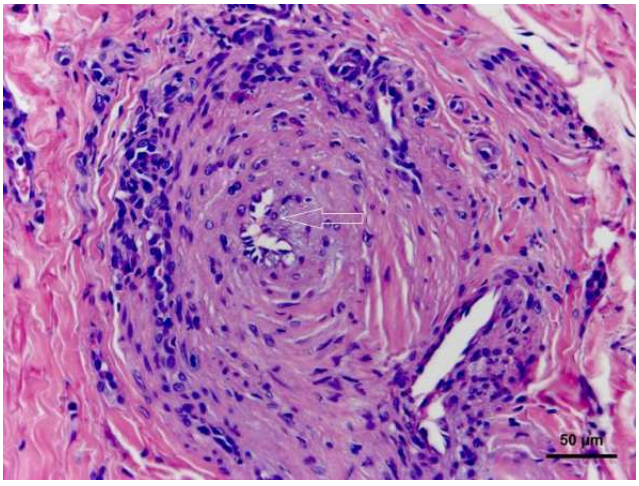


Figure 6. Deep dermis, large arteriole. Subendothelial deposition of extracellular basophilic myxoid matrix and partial luminal occlusion (arrow). Perivascular lymphocyte cuff. Hematoxylin and eosin, Bar = 50 µm.

Discussion

Canine proliferative arteritis of the nasal philtrum appears to be an uncommon or perhaps underdiagnosed disease with case reports summarized in Table 1 (1, 4, 5, 6, 8). Saint Bernard dogs are overrepresented among all reports, suggesting a possible inherited component. However, the lack of epidemiological studies precludes a reasonable conclusion. Here, for the first time, were described the disease in a previously unreported breed, i.e., Brazilian Mastiff. Patient of case 2 was diagnosed at the age of 1-year, suggesting that this disease can also occur in younger dogs, contrary to the exclusively later onset between 3 and 6 years-old reported by Torres *et al.* (6).

The main clinical feature reported is a single ulcer located on the nasal philtrum, with or without episodes of arterial hemorrhaging (1, 4, 5, 6, 8). When bleeding or associated changes (i.e. anemia and weight loss) are present, a surgical approach is highly desirable in order to control hemorrhaging and avoid clinical worsening (5, 8). However, the success rate of surgery alone is questionable. Pratscheck and Hill (5) reported no recurrence of clinical lesion during a 34-month period after a surgical procedure in one dog. However, another dog required adjuvant treatment with tacrolimus after four years of surgery (8). Similarly Vuolo *et al.* (8) found no recurrence after combining surgery and clinical treatment with cyclosporine, fish oil, vitamin E, and pentoxyfiline (5).

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Table 1. Summary of cases previously described in the literature, organized by age, sex, breed and treatment.

Patients (n)	Age (years)	Sex	Breed	Treatment	Reference
4	5	M	Saint Bernard	Oral (prednisone 1.1 mg/Kg)	(6)
	9	F	Saint Bernard	Oral (prednisone 1.1 mg/kg; tetracycline 500 mg; niancinamide 500 mg; and fish oil)	
	6	M	Saint Bernard	Oral (prednisone 1.1 mg/kg	
	5	F	Giant Schnauzer	Topical (flucinolone in dimethyl sulfoxide)	
2	4	M	Basset Hound	Surgical	(5)
	3	F	Basset Hound	Surgical	
1	6	M	Samoyeda	Oral (pentoxyfiline 25mg/kg)	(1)
1	6	M	Saint Bernard	Topical (2% cyclosporine); oral (prednisone)	(4)
1	4	M	Saint Bernard	Topical (0.1% tacrolimus); oral (prednisone 0.5 mg/kg) Surgical *After surgery:* topical (0.1% tacrolimus); oral (cyclosporine 4 mg/kg; pentoxfylline 9.8 mg/kg; and fish oil)	(8)

Patients with mild lesions may benefit from a long-term clinical treatment with immunosuppressive drugs. Prednisolone, cyclosporine and/or topical tacrolimus demonstrate satisfactory results, as we also observed in case 2 (4, 5, 6, 8). Drugs that enhance local blood supply (e.g. pentoxifylline), modulate the production of endogenous steroids (e.g. niancinamide) and exert anti-inflammatory effects (e.g. fish oil) can also be used (1). Case 1 did not have any clinical improvement after clinical treatment. A possible reason for this would be related to the degree of fibroblastic and myofibroblastic proliferation observed in arterioles. Indeed, case 1 presented more prominent spindle cell proliferation than case 2. Since immunosuppressive drugs suppress vascular inflammation rather than myofibroblast proliferation, a surgical approach might be indicated in more advanced cases.

Nasal ulcers are reported in immune-mediated, traumatic, neoplastic and infectious diseases. The typical linear or V-shaped configuration is highly suggestive of proliferative arteritis (2). However, other diseases can display similar lesions in this region as described by Torres *et al.* (6). Thus, histopathology is required for a definitive diagnosis (6). A wide range of epidermal, dermal and vascular changes are reported. Most prominent among them are those found in dermal arterioles, which display a subendothelial spindle cell proliferation, extracellular deposition of glycosaminogyclans (GAG), mural neutrophilic or lymphocytic arteritis and/or perivascular lymphocyte cuffs (2, 4, 5, 6, 8).

The major cellular and ECM components of the vascular wall are endothelial cells, smooth muscle cells, collagen, elastin, fibronectin, and GAG (3). GAG are synthetized by endothelial and smooth muscle cell, and participate in arterial viscoelasticity, permeability, hemostasis and lipid metabolism (9). The levels of vascular GAG undergo changes with aging or in vascular diseases such atherosclerosis and hypertension. The final consequence is the remodeling of the vessel wall (3, 7, 10).

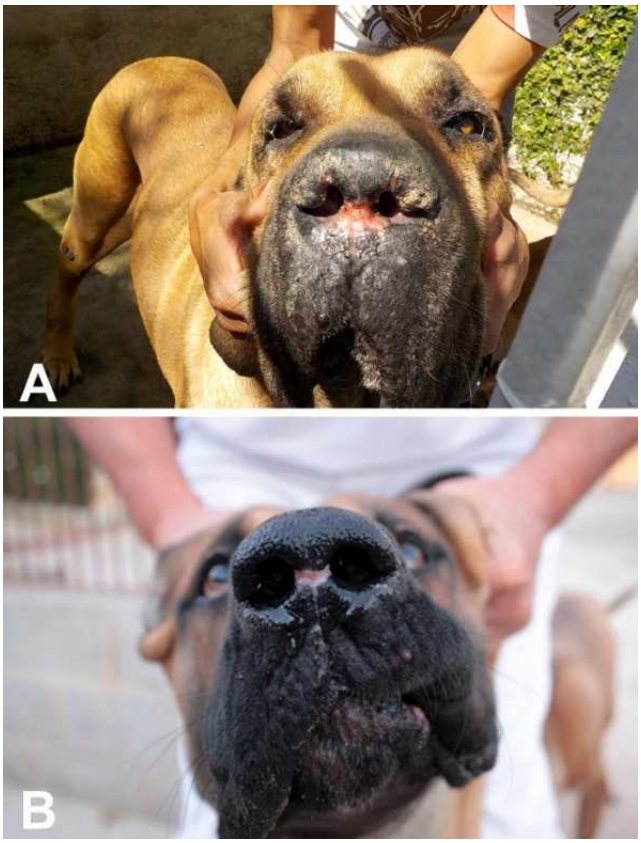


Figure 7. A. Case 1. No clinical improvement was noted after treatment with prednisone and tacrolimus. The ulcer is still present. **B.** Case 2. Mild clinical improvement with reduction in the height of the ulcer.

Proliferative arteritis in dogs presents microscopic similarities to early stages of atherosclerosis where there is intimal GAG deposition and smooth muscle proliferation (9). Although we were unable to perform immunohistochemistry in order to determine the origin of spindle cells other authors verified a smooth muscle immunophenotype in this cell population (3, 4, 6, 10).

Interface and lichenoid dermatitis are diagnostic clues for immune-mediated skin diseases. Interface dermatitis is defined as a minimal to mild superficial dermal inflammation with vacuolar degeneration of basal cells and/or apoptosis of keratinocytes. Intense, band-like subepidermal inflammation typifies lichenoid dermatitis (2). Mild interface vacuolar dermatitis and interface lichenoid dermatitis inflammation were observed and other authors suggest that immune-mediated mechanisms can also be involved in disease progression and/or initiation. However it is important to note that vacuolar degeneration of basal cells when mild and scattered, can be a normal finding (2). In conclusion, proliferative arteritis is an uncommonly reported disease in veterinary dermatology. Infectious, traumatic, neoplastic and immune-mediated diseases should be considered in a differential diagnosis. For a conclusive diagnosis, it is essential to associate clinical signs and histopathological changes, as described previously. The choice for surgical and/or clinical treatment must take into account the severity of signs and long-term management. Topical and systemic treatments with immunosuppressive and immunomodulatory drugs can be used alone or together with surgery.

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