Arch Med Vet **47, 255-258 (2015)**

COMMUNICATION

Proliferative arteriopathy of the nasal philtrum in a Saint Bernard dog. Case report

Arteriopatía proliferativa del filtro nasal en un perro San Bernardo: Reporte de caso

I Pereira[a], R Gómez[a] , S Anticevic[b], D Rossel[a], V Aránguiz[a], FR Carvallo[c*]

[a]Small Animal Veterinary Hospital, Faculty of Veterinary Sciences, University of Chile, Santiago, Chile.

[b]Department of Clinical Sciences, Faculty of Veterinary Sciences, University of Chile, Santiago, Chile.

[c]Department of Animal Pathology, Faculty of Veterinary Sciences, University of Chile, Santiago, Chile.

RESUMEN

La remodelación vascular debido a la proliferación de células de músculo liso es una respuesta estereotípica al daño de vasos sanguíneos, sin importar la causa. Aquí se reporta el caso de dermatitis ulcerativa localizada de un perro San Bernardo debido a una arteropatía proliferativa del filtro nasal. En este caso se observa la presencia de células positivas a vimentina y actina de músculo liso que proliferan desde la media hacia la subíntima de las arterias de pequeño y mediano calibre. Se discute la presentación clínica, el diagnóstico, la patogénesis probable y el desenlace clínico de este caso.

Palabras clave: arteritis, músculo liso, media vascular, immunosupresores.

SUMMARY

Vascular remodeling due to medial smooth muscle cell proliferation is a stereotypical response to vascular damage, regardless of the cause. Here, a case of ulcerative dermatitis due to localised proliferative arteriopathy of the nasal philtrum of a male Saint Bernard dog is reported. The presence of vimentin and smooth muscle actin positive cells proliferating from the media into the subintima of medium and small sized arteries was observed. Clinical presentation, diagnosis, probable pathogenesis and outcome are discussed.

Key words: arteritis, smooth muscle, vascular media, immunosuppressant.

INTRODUCTION

Vascular smooth muscle cells (SMCs) are a major component of the media of blood vessels. These cells have a contractile phenotype, and its primary function is to the vascular tone. When terminally differentiated, these cells proliferate at an extremely low rate, display a low synthetic activity and express a unique set of contractile proteins, such as smooth muscle myosin heavy chain, smooth muscle α-actin, SM22α, calponin and others (Owens *et al* 2004). Nevertheless, intimal thickening due to proliferation of SMCs is a stereotypical response to vessel wall damage, irregardless of the cause (Mitchell and Schoen 2010). In this study, a case of localised proliferation of SMC of small and medium sized arteries at the nasal philtrum of a dog is reported.

MATERIAL AND METHODS

A 6 year-old, male Saint Bernard dog was received for clinical examination, with the complaint of spontaneous and continuous bleeding of the nostrils. The clinical history outlined the presence of a nasal lesion when this patient was young, though no diagnostic workout was performed at the time. Clinical examination revealed that bleeding proceeded from the nasal planum, specifically at the base of the nasal philtrum. In this area, a linear, non pigmented, ulcerative lesion was present, which conferred an aspect similar to a traumatic lesion. All the other parameters at the physical examination were unremarkable. A full blood work and a biopsy were suggested, aiming to rule out an autoimmune disease (discoidal lupus), a traumatic event or proliferative arteritis of the nasal philtrum. Pre-surgical hematology and blood chemistry exams were unremarkable.

Samples of skin of the affected area were fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Five micrometer sections were stained with hematoxylin and eosin, Alcian blue pH 2,5 and Masson trichromic stain. Additionally, formalin-fixed, paraffin-embedded sections of skin were subjected to immunohistochemical staining for Vimentin (25 µg/mL, mouse monoclonal vimentin V9, Ventana®, Tucson, Arizona), smooth muscle actin (0.02 µg/mL, mouse monoclonal HUC1-1, Ventana®, Tucson Arizona) and CD34 (1µg/mL, mouse monoclonal QBEnd/10, Ventana® Tucson, Arizona). This was performed on the BenchMark GX Slide Staining System (Ventana®, Rotkreuz, Switzerland) Automated Staining System. Secondary antibody and detection was performed

Accepted: 30.10.2014.

* Santa Rosa 11735, La Pintana, Santiago, Chile; francisco.carvallo@gmail.com

with the ultra-view Universal DAB detection kit (Ventana, Tucson, Arizona). The primary antibody was replaced with buffer in negative control sections, which consisted of a section of canine skin with no lesions.

RESULTS AND DISCUSSION

In the skin, the epidermis was ulcerated. In the dermis, all inflammatory changes were associated with the presence of a skin ulcer, with numerous neutrophils, macrophages and granulation tissue, characterised by new vessel formation and fibrosis. The subintima of arteries and arterioles of the superficial and deep dermis adjacent to the ulcer, revealed marked proliferation of spindle cells immersed in an eosinophilic loose matrix (figure 1a). This proliferation occluded partially the vascular lumen and occasionally, fibrin thrombi were found attached. In small vessels, there was occasional fibrinoid degeneration of the vascular wall. Masson trichromic stain revealed the presence of small amounts of collagen between proliferative spindle cells of small and medium caliber blood vessels, and Alcian blue pH 2.5 stain highlighted the presence of acid mucin. These spindle cells were Vimentin and Smooth muscle actin positive (figure 1b) and CD34 negative.

After the biopsy surgery, this patient was treated with oral prednisone and 2% ciclosporine ointment. Ten days after the onset of the treatment, the patient was examined. After a month, the owner commented that the lesion had not bled again, although it seem to be the same size as the first day of treatment. The patient was otherwise healthy. Together, histopathological, immunohistochemical and clinical findings are consistent with proliferative arteritis of the nasal philtrum.

There are several disorders that can affect the nasal plane of dogs, including immune mediated diseases, such as pemphigus vulgaris and discoid lupus erythematosus; neoplastic diseases, such as epitheliotropic lymphoma; infectious diseases, particularly Leishmaniasis; contact hypersensitivity; and certain idiopathic conditions (Ginn *et al* 2007). However, none of these disorders is known to exclusively affect the nasal philtrum. Proliferative arteritis of the nasal philtrum is an uncommon and distinctive vascular disease, and is the only entity reported to selectively affect this particular anatomic position (Scott *et al* 2001, Gross *et al* 2005). This disease has been described more frequently in the Saint Bernard breed, which initially led to the suggestion that this condition could be inherited (Torres *et al* 2002, Gross *et al* 2005). Nevertheless, it has been also reported in adult giant Schnauzers, Basset hounds and a Newfoundland, suggesting that other factors could be involved in the pathogenesis (Torres *et al* 2002, Pratschke and Hill 2009). The onset of clinical signs is typically between 3 and 6 years of age, and is characterised by the presence of solitary ulcers of the nasal philtrum. Lesions are usually neither pruritic nor painful and, generally, affected animals are otherwise healthy. This entity occurs with episodes of arterial bleeding (Gross *et al* 2005), which can lead to anemia. In this case, clinical findings, and gross and histological lesions are similar to the cases reported above, with the exception that anemia was not noted.

The proliferation of cells within the vessel wall is a major contributor to arterial remodeling. In the presence of endothelial damage or dysfunction, regardless of the cause, SMCs lose their ability to contract and display a novel phenotype. Smooth muscle cells can proliferate and produce extracellular matrix (collagen and fibronectin),

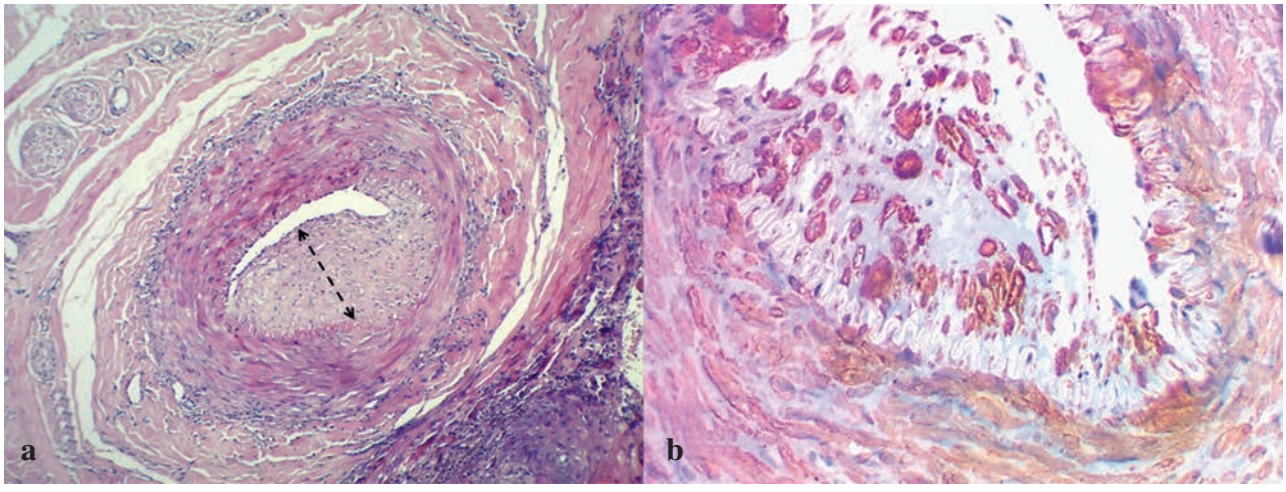

Figure 1. a) Superficial dermal artery, nasal philtrum. There is moderate expansion of the media into the subendothelial area, which partially occludes this vessel (discontinued arrow). H&E stain, 100X. b) Superficial dermal artery, nasal philtrum. The cytoplasm of proliferative spindle cells displays cytoplasmic immunostain for smooth muscle actin. Hematoxylin counterstain, 400X.

a) Arteria de la dermis superficial, filtro nasal. Hay expansión moderada de la media vascular en el área subendotelial, la que parcialmente obstruye este vaso sanguíneo (línea discontinua).Tinción H&E, 100X. b) Arteria de la dermis superficial, filtro nasal. El citoplasma de las células fusiformes proliferativas muestra inmunotinción citoplasmática para actina músculo liso. Contratinción de hematoxilina, 400X.

in the same way fibroblasts fill in a wound (Shi and Shen 2014). This proliferation would thicken the intima of vessels, which is known as a neo intima (Mitchell and Schoen 2010), and is accompanied by fragmentation and degradation of elastin, which adversely affects the biomechanical properties of blood vessels. Synthetic SMCs also generate matrix metalloproteinases that facilitate the migration from the media to the intima, by detaching these cells from the extracellular matrix (Durante 2013). Migratory, proliferative and synthetic activities of neo intimal SMCs are regulated by products derived from platelets, endothelial cells and macrophages, as well as by activated coagulation and complement factors. Promoters include Platelet derived growth factor, endothelin-1, interferon-γ and interleukin-1. Inhibitors include heparan sulfates, nitric oxide and Transforming Growth Factor-β (Berk 2001). With time, the neointimal SMCs restore to a non-proliferative state, but thickening is permanent. If the stimulus is persistent or recurrent, narrowing and stenosis of affected vessels will develop, with consequent ischemia and necrosis of irrigated tissues (Mitchell and Schoen 2010). In humans, arterial remodeling is a prominent feature of several vascular disorders, such as atherosclerosis, restenosis after percutaneous coronary intervention, post-transplant vasculopathy, systemic and pulmonary hypertension and aortic aneurysm and dissection (Durante 2013). In veterinary medicine, disseminated conditions such as arteriosclerosis, atherosclerosis and hypertension can show marked vascular remodeling. Local conditions such as sclerosis of the pulmonary artery due to *Dirofilaria immitis* or remodeling of the cranial mesenteric artery due to *Strongylus vulgaris* have been reported (Maxie and Robinson 2007), but in this particular case, no association with an infectious or degenerative condition could be made. Torres *et al* (2002) postulated that the primary lesion is inflammation of arteries and arterioles of the nasal philtrum, leading to proliferation of vimentin and smooth muscle actin positive spindle cells and the deposition of extracellular matrix, with thickening of the vascular subintima. With time, there is hypoperfusion due to partial occlusion, causing local ischemia, necrosis and ulceration of the overlying skin. The vasculopathy may also cause weakness of the vascular walls with subsequent rupture. In this case, the presence of smooth muscle cells in the subintima partially occluding the vascular lumen, was demonstrated by immunohistochemistry (vimentin and smooth muscle actin positive). Regarding the inflammatory component evidenced in the upper dermis, this was mostly associated to the ulcerative skin condition, without inflammatory cells in the vascular wall. Because of this, we call this condition an arteriopathy.

Treatment for this condition has involved parenteral and topical medication with long term immunosuppressant therapy. Frequently, discontinuation of treatment has led to recurrence of clinical signs (Torres *et al* 2002, Gross *et al* 2005). In this particular case, prednisone and topical cyclosporine were used, both with strong immunosuppressant activity. Pratschke and Hill (2009) proposed an initial strategy using tacrolimus ointment. If these treatments prove to be unsuccessful, non-curative or too expensive for long term use, a surgical intervention should be considered as a viable and curative option.

Although proliferative arteritis of the nasal philtrum is a rare disease, the diagnosis is relatively simple because of the specific location, racial bias (mostly Saint Bernard dogs) and typical histopathologic lesions (skin ulcer with dermal vascular proliferative arteritis/arteriopathy, consisting of smooth muscle cells). It has been demonstrated that induction therapy with prednisone followed by local application of cyclosporine ointment is an effective solution to prevent the onset of short-term injuries. The cause of this condition still needs to be elucidated.

ACKNOWLEDGEMENTS

The authors acknowledge Mrs. Sue Ellen Uzal and Dr. Francisco Uzal for the English review of this manuscript, and Mr. Miguel Sepulveda and Mr. Jorge Vergara Borquez for the performance of histochemical and immunohistochemical stains.

REFERENCES

Berk B. 2001. Vascular smooth muscle growth: autocrine growth mechanisms. *Physiol Rev* 81, 999-1030.

Durante W. 2013. Role of arginase in vessel wall remodelling. *Front Immunol* 4, 1-12.

Ginn PE, JKEL Mansell, PM Rakich. 2007. Skin and appendages. In: Maxie MG (ed). *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol 1. 5th ed. Saunders Elsevier, Philadelphia, PA, USA, Pp 553-782.

Gross TL, PJ Ihrke, MJ Walder, VK Affolter. 2005. Vascular diseases of the dermis. In: *Skin diseases of the dog and cat: Clinical, Histopathologic Diagnosis*. 2nd ed. Blackwell, Ames, IA, USA, Pp 238-260.

Maxie MG, WF Robinson. 2007. Cardiovascular system. In: Maxie MG (ed). *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol 3. 5th ed. Saunders Elsevier, Philadelphia, PA, USA, Pp 1-106.

Mitchell RN, FJ Schoen. 2010. Blood vessels. In: Kumar V, Abbas A, Fausto N, Aster JC (eds). *Robbins and Cotrans Pathologic basis of diseases.* 8th ed. Saunders Elsevier, Philadelphia, PA, USA, Pp 487-528.

Owens GK, MS Kumar, BR Warmhoff. 2004. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. *Physiol Rev* 84, 767-801.

Pratschke KM, PB Hill. 2009. Dermal arteritis of the nasal philtrum: Surgery as an alternative to long-term medical therapy in two dogs. *J Small Anim Pract* 50, 99-103.

Shi N, SY Chen. 2014. Mechanisms simultaneously regulate smooth muscle cells proliferation and differentiation. *J Biomed Res* 28, 40-46.

Scott DW, WH Miller, CE Griffin. 2001. Miscellaneous skin diseases. In: *Small Animal Dermatology*. 6th ed. WB Saunders, Philadelphia, PA, USA, Pp 1125-1183.

Torres SM, TO Brien, DW Scott. 2002. Dermal arteritis of the nasal philtrum in a Giant Schnauzer and three Saint Bernard dogs. *Vet Dermatol* 13, 275-281.