ABSTRACT. A 10-year-old female spayed American Pit Bull Terrier was presented with a slow growing mass on the temporal limbus area of the right eye. Canine nodular granulomatous episclerokeratitis was suspected, and the affected eye was treated with 1% prednisolone acetate ophthalmic suspension and 0.03% Tacrolimus ophthalmic solution. As the lesion did not respond to the medical treatments and continued to grow, the mass was excised by lamellar sclerokeratectomy. Microscopically, the mass was composed of granulomatous inflammation with intrathiocytic lipids and lakes of acicular cholesterol clefts, histopathology findings consistent with xanthogranuloma. To the authors’ knowledge, this is the first canine report of limbal xanthogranuloma. The purpose of this report is to describe the clinical and histopathological findings on a dog affected by limbal xanthogranuloma. To the authors’ knowledge, this is the first reported case of limbal xanthogranuloma in a dog.

Xanthogranulomas, also known as xanthomas, are inflammatory lesions resulting from the accumulation of lipid-laden macrophages, giant cells and cholesterol in tissue [3, 19]. Cutaneous xanthogranulomas are single to multiple nodular lesions rarely occurring in dogs and cats [3, 19]. Formation of cutaneous xanthogranulomas reflects dyslipidemia in most cases; however, other cases, particularly solitary lesion, are idiopathic [15, 19]. In humans, juvenile xanthogranuloma (JXG) occurs predominantly in infants and young children, and is a benign inflammatory condition of unclear etiology that can affect any organ [14]. Approximately 10% of JXG affected human individuals have ocular manifestations [21], mainly involving the iris that could be associated with hyphema and secondary glaucoma [18]. Sporadically, JXG presents as a solitary limbal lesion in juvenile as well as adult individuals (adult-onset xanthogranuloma) [4, 14, 16, 18]. Thirty five human cases of xanthogranuloma involving the limbus have been reported to the authors’ knowledge [4, 14, 16, 18]. Although JXG often occurs in infants and children, of the 35 cases involving the limbus, five cases occurred in teenagers and 10 cases occurred in adults (adult-onset xanthogranuloma) [4, 14, 16, 18]. The purpose of this report is to describe the clinical and histopathological findings on a dog affected by limbal xanthogranuloma. To the authors’ knowledge, this is the first reported case of limbal xanthogranuloma in a dog.

A 10-year-old female spayed American Pit Bull Terrier was presented to BluePearl-Chesterfield-Midwest Veterinary Referral Center with a 7 × 5 × 3 mm sized, non-painful, tan yellow, well-vascularized exophytic sessile mass affecting the temporal limbus of the right eye (OD) (Fig. 1). Prior to the presentation, the affected OD was treated by a previous veterinary ophthalmologist with tacrolimus aqueous ophthalmic solution and neomycin, polymyxin and dexamethasone ophthalmic suspensions (b.i.d.) for presumed canine nodular granulomatous episclerokeratitis (NGE) for 6 months. The left eye (OS) had been enucleated for an unknown reason by the time the owner adopted the dog from a rescue group when she was 2-year-old. Based on the gross appearance of the mass and its location, NGE was again suspected. Surgical excision or intralesional steroid injection was discussed, but was declined by the owner, and the lesion was continuously treated medically alone by 0.03% tacrolimus aqueous ophthalmic solution and neomycin, polymyxin and dexamethasone ophthalmic suspensions (b.i.d.) for 14 months. The lesion did not respond to the topical treatments and continued to grow slowly over the course of 14 months. With the owner’s consent, the mass was eventually excised under general anesthesia by lamellar sclerokeratectomy for treatment and histopathological diagnosis. A conjunctival advancement graft was placed over the deeper sclerokeratectomy site. The excised mass was placed in 10% neutral buffered formalin. After routine histologic processing, 5-µm-thick sections stained with H&E were evaluated.

Histologically, the affected corneoscleral stroma was replaced and expanded by an ill-demarcated granulomatous inflammatory focus with lakes of acicular cholesterol clefts and occasional subepithelial basophilic granular mineral deposits (Fig. 2a). These mineral deposits were calcification as confirmed by positive Alizarin-Red staining (not shown). The overlying corneal epithelium was hyperplastic. Granulomatous inflammation was characterized by numerous foamy macrophages, fewer lymphocytes, plasma cells and multinucleated giant cells. These foamy cells stained positively for CD18, a leukocyte marker (University of Missouri) with xanthogranuloma.
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California, Davis, CA, U.S.A., CA16.3C10, 1:120 dilution) (not shown), and ionized calcium binding adapter molecule 1 (Iba1), a macrophage marker (WAKO, Richmond, VA, U.S.A., 019–19741, 1:1,000 dilution) (Fig. 2b), while stained negatively for S100, a Langerhans cell marker (Dako, Carpentaria, CA, U.S.A., Z0311, 1:800 dilution) (Fig. 2c) by immunohistochemistry, confirming they were macrophages. Multinucleated giant cells had up to 15 nuclei that were arranged randomly and centrally (foreign body type) (not shown) and arranged peripherally at one pole (Langhans type) (Fig. 2d). Rarely large macrophages that had a central eosinophilic homogeneous cytoplasm surrounded by foamy cytoplasm with more than 1 variably discernible nuclei, resembling Touton type giant cells, were observed among infiltrates of foamy macrophages (Fig. 2e). Frozen sections were additionally

Fig. 1. Clinical appearance of a tan yellow, well-vascularized nodular mass on the temporal limbal area of the right eye (OD) on initial presentation.

Fig. 2. Photomicrographs of limbal xanthogranuloma. (a) The lesion is composed of granulomatous inflammation with numerous foamy macrophages admixed with lakes of acicular cholesterol clefts (asterisks). Occasionally, there are subepithelial mineral deposits (arrows). The overlying corneal epithelium is hyperplastic. H&E. Bar=200 µm. (b) Foamy macrophages stain positively for Iba1. Immunohistochemistry. Bar=100 µm. (c) Foamy macrophages stain negatively for S100. Immunohistochemistry. Bar=100 µm. (d) Multinucleated giant cells including Langhans type giant cells (arrow) are seen among infiltrates of foamy macrophages. H&E. Bar=50 µm. (e) There are rare large macrophages that have a central eosinophilic homogeneous cytoplasm surrounded by foamy cytoplasm with multiple variably discernible nuclei, similar to Touton type giant cells (arrow) among infiltrates of foamy macrophages. H&E. Bar=50 µm. (f) There are intralobesional and intracytoplasmic lipids. Oil Red O. Bar=50 µm.
prepared from the remaining formalin-fixed specimen and stained positively with Oil Red O, confirming the presence of intracytoplasmic lipid droplets (Fig. 2f). Special stains including Gomori’s methenamine silver, periodic acid Schiff and Fite’s acid fast showed no fungal organisms or mycobacteria (not shown). No foreign body was noted. Histologically, the clinical diagnosis of NGE was not supported as the lesion consisting of cellular infiltrates dominated by lipid-laden foamy macrophages with cholesterol deposits is not typical of NGE where the lesion is usually a well-demarcated granulomatous inflammation composed of a mixture of lymphoplasmacytic inflammatory cells and macrophages-histiocytic cells. Based on the location and the histopathologic characteristics of the lesion, limbal xanthogranuloma was diagnosed.

Postoperatively, the dog was treated with ophthalmic suspensions including 0.3% ofloxacin (t.i.d.) for 2 weeks, 1% prednisolone acetate (b.i.d.) and 0.03% tacrolimus (t.i.d.) for 4 weeks. Over the course of following 2 months ophthalmic suspension of 1% prednisolone acetate was tapered to twice a week and 0.03% tacrolimus was reduced to once daily, and maintained these thereafter. There was no evidence of recurrence at 6 months following surgical excision with ancillary steroid and tacrolimus ophthalmic suspensions. Although there was no recurrence, a subepithelial thin white grainy plaque, the lesion compatible with calcification and increased vascularity remained at the surgery site (Fig. 3).

Adult-onset xanthogranuloma in humans is one of the four, rare and poorly understood syndromes involving the ocular tissue called adult orbital xanthogranulomatous disease [10]. Adult-onset asthma and periocular xanthogranuloma, necrobiotic xanthogranuloma, and Erdheim-Chester disease are the other three syndromes included in adult orbital xanthogranulomatous disease, and these are all histologically diagnosed by demonstrating characteristic xanthogranulomatous inflammation [10]. The majority of human cases of limbal xanthogranuloma in both children (JXG) and adults (adult-onset xanthogranuloma) had a unilateral solitary lesion and were not associated with other xanthogranuloma lesions. Skin lesions were recognized in only one adult case [17] and 3 cases in children [5, 21]. No other xanthogranuloma lesions were noted by physical examination in this canine patient.

Ocular manifestations of xanthogranulomas are extremely rare in small animal medicine, and only one report of intraocular xanthogranulomas in 3 Miniature Schnauzer dogs [20] and only one canine case of xanthogranuloma involving the palpebral conjunctiva [3] have been reported to the authors’ knowledge. The previously reported 3 Miniature Schnauzer dogs with intraocular xanthogranuloma all had clinical history of diabetes mellitus and hyperlipidemia [20]. The dog reported in the present study was in good body condition, bright, alert, responsive and had been fed a commercial dog food with an adequate fat content; however, because of the clinical information of the Miniature Schnauzer intraocular xanthogranuloma cases [20] and because formation of xanthogranuloma can reflect dyslipidemia [9], plasma concentrations of total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL) and glucose, and serum concentrations of T4 and thyroid-stimulating hormone (TSH) were examined after histopathologic diagnosis of limbal xanthogranuloma was made in this case. Total cholesterol was 296 mg/dl (normal reference range 133–338 mg/dl), triglycerides was 53 mg/dl (normal reference range 10–355 mg/dl), HDL was 187 mg/dl, and LDL was 6 mg/dl. Concentrations of total cholesterol and triglycerides were within normal reference ranges of the University of Missouri’s Veterinary Medical Diagnostic Laboratory. Although there were no established reference intervals for HDL and LDL in dogs, the HDL and LDL concentrations were not alarming. The plasma concentration of glucose (78 mg/dl, normal reference range 76–119 mg/dl) and serum concentrations of T4 (1.4 µg/dl, normal reference range 0.1–4.0 µg/dl) and TSH (0.24 ng/ml, normal reference range 0.1–0.6 ng/ml) were also within normal reference ranges. The dog in this report did not have any clinical evidence of hyperlipidemia, diabetes mellitus or hypothyroidism. Plasma lipid profile was not evaluated in the previously reported feline conjunctival xanthogranuloma case [3]. Of the 35 human xanthogranuloma cases involving the limbus, no dyslipidemia nor diabetes mellitus was reported except for a 43 year-old male individual who was diabetic with associated multiple endocrine neoplasia (MEN) type I [1].
It is known that some keratopathies can be associated with corneal cholesterol-lipid deposits in dogs. Corneal lipidosis (crystalline stromal dystrophy, lipid dystrophy) is the most common type of corneal lipidic deposition in dogs [2]. It often affects young-adult dogs and presents as a bilateral, relatively symmetrical corneal opacity which develops mainly in the central part of the cornea with no or very limited vascular in-growth [8]. Hereditary has been suspected for corneal lipidosis in some breeds [2]. Arcus lipoides corneae is another corneal lipid deposit condition. It is typically bilateral and associated with systemic metabolic diseases, such as hypothyroidism [8]. Lipid deposition may also occur in the corneal stroma at the margins of localized corneal diseases, such as NGE and trauma [8]. Although the cause of limbal xanthogranuloma in this dog was unknown, no evidence of hyperlipidemia, diabetes mellitus or hypothyroidism implies that the lesion in this case might have stemmed from a localized corneal disease process where spillage of lipids and cholesterol provoked xanthogranulomatous inflammation.

Diagnosis of xanthogranuloma should be based on the characteristic histopathology of accumulation of lipid-laden foamy macrophages admixed with giant cells and cholesterol clefts. In human cases, the main differential diagnosis for limbal xanthogranuloma is Langerhans cell histioctysis, also known as histiocyteosis X [19]. Limbal xanthogranulomas are typically distinguished from Langerhans cell histiocyteosis by negative immunostaining for S100 and positivity for macrophage markers [19]. Immunohistochemical findings in this canine case are compatible with human limbal xanthogranuloma cases. Of total 14 adult and teenager cases of limbal xanthogranulomas underwent surgical excision with or without ancillary local steroid treatments, local recurrence occurred in 4 cases, all within 6 months after excisional biopsy [6, 7, 11, 13]. Lamellar keratectomy has been recommended for adult-onset xanthogranuloma in humans and was effective in this canine case. Supplementary treatment with topical steroid may be necessary as in some human cases [11, 12, 16].

Xanthogranuloma should be considered a differential diagnosis of a limbal mass refractory to topical steroid treatments in the dog. Limbal xanthogranuloma in this canine patient shares many similarities with adult-onset xanthogranuloma in human patients. Surgical excision should be initiated to diagnose limbal xanthogranuloma and prevent potential growth toward the center of the cornea with sight-threatening and secondary subepithelial calcium deposits (dystrophic calcification) such as seen in this case. The role of dyslipidemia in the disease process of limbal xanthogranuloma was not supported in this case; however, examinations of the plasma lipid profile, glucose level and thyroid panel would be prudent in future ocular xanthogranuloma cases for further elucidation of the disease mechanism of this rare condition in the dog.

REFERENCES