Unusual presentation of a mesenchymal eyelid hamartoma and an update of the incidence of periocular hamartomas in dogs

Ongewone presentatie van een mesenchymaal ooglidhamartoma en een overzicht van het voorkomen van perioculaire hamartomen bij de hond

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ABSTRACT

A mesenchymal hamartoma in the dorsomedial eyelid of a Staffordshire bull terrier and the incidence and histological features of twenty-two canine mesenchymal periocular hamartoma cases are reported. The archives of the “Comparative Ocular Pathology Laboratory” of Wisconsin (USA) were searched for canine mesenchymal periocular hamartoma. Signalment, clinical appearance, location and histological findings are summarized for twenty-two dogs, containing fourteen different breeds, between four and fourteen years old. Fifteen hamartomas were located at the lateral canthus. Histologically, they consisted of fully differentiated fibrous tissue interspersed with adipose tissue, with bundles of skeletal/smooth muscle in ten cases, and peripheral nerve tissue in two cases. No mitotic figures were noted. Mesenchymal hamartomas may present as a subcutaneous, subconjunctival or orbital mass. Although they have a predisposition to occur at the lateral canthus, they may be located elsewhere on the eyelids or in the orbit.

SAMENVATTING


INTRODUCTION

A hamartoma is an excessive but focal overgrowth of cells and tissues native to the organ, in which it occurs. The cellular elements are mature and identical to the remainder of the organ, but they do not reproduce the normal architecture of the surrounding tissue. They can develop in any organ or tissue, and are regarded by some authors as a form of tissue proliferation midway between a malformation and a true neoplasia (Kumar et al., 2013). Histologically, they may show an alteration of a single cell line or of multiple related cell lines (Poomeechaiwong and Golitz, 1990).
Hamartomas have been sporadically reported in dogs and have been described in several anatomical locations, including neurologic structures (spinal cord, brain and cranial nerves) (Cook, 1977; Smith and Van Winkle, 2001; Sanders et al., 2002; Sanders, 2007; Ide et al., 2009; Sakurai et al., 2011; Sebastianelli et al., 2013), periodontal ligament (Tanev et al., 2005), nasal cavity and frontal sinus (Leroith et al., 2009), lungs (Njoku et al., 1972; Watson et al., 1993; Takahashi et al., 2000), pulmonary artery (Chanoit et al., 2012), liver (McGavin and Henry, 1972; Boorer, 2008; Gualtieri et al., 2009), spleen (Matos et al., 2007), kidney (Splitter et al., 1972), intestines (Brown et al., 2007; Bemelmans et al., 2011), genitalic system (Fry et al., 2003; Beccaglia et al., 2008), placenta (Cushing et al., 2011), flexor muscle of the carpus (Corzo-Menéndez et al., 2001), and skin including the eyelids (Callan et al., 2005; Kafarnik et al., 2010; Yasuno et al., 2011).

In the human-based literature, hamartomas have been described as a single-eyelid or conjunctival hamartoma without other ocular lesions or as part of a clinical syndrome. Reported solitary hamartomas of the eyelid include rhabdomyomatous mesenchymal hamartoma (Read et al., 2001), fibrous hamartoma (Bradfield et al., 2007), pigmented hamartoma with apocrine, follicular and sebaceous differentiation (Proia, 2007), striated muscle hamartoma (Harris et al., 2008), congenital smooth muscle hamartoma (Johnson and Jacobs, 1989), and basaloïd follicular hamartoma (Jakobic et al., 2012). Congenital smooth muscle hamartomas of the conjunctiva have been rarely reported in human medicine (Roper et al., 1999; Mora et al., 2012).

Mesenchymal hamartomas have rarely been reported in veterinary medicine (Wang et al., 2001; Brown et al., 2007; Kafarnik et al., 2010; Greci et al., 2011). They have been described in the liver of a cat and a horse (Wang et al., 2001; Brown et al., 2007). Recently, inflammatory polyps of the nasal turbinates of cats have been termed feline mesenchymal nasal hamartoma consistent with its human counterpart described in children (Greci et al., 2011). Kafarnik (2010) described mesenchymal hamartomas as benign lesions of the canine eyelid with a predisposition for the temporal canthus.

In the present paper, the unusual presentation of a mesenchymal hamartoma in the dorsomedial eyelid of a dog is reported. The purpose of the second, retrospective part of the study is to document the incidence and histopathological features of twenty-two canine mesenchymal periocular hamartomas. The present study is a continuation of the study of Kafarnik (2010), updated with twelve new cases.

**MATERIALS AND METHODS**

The case report describes in detail the clinical history, ocular examination, surgery and histopathology of a hamartoma in the medial aspect of the upper eyelid in a Staffordshire bull terrier.

The archives of the “Comparative Ocular Pathology Laboratory” of Wisconsin (USA)(COPLOW) were searched for canine mesenchymal periocular hamartoma, during the period of January 2001 till December 2013. Twenty-two canine mesenchymal hamartomas were identified, including the present case report of the Staffordshire bull terrier (case 19). Clinical information was retrieved from the submission requests. Signalment, clinical appearance, location, and histological findings were evaluated for each case. All tissues were fixed in 10% buffered formalin. Paraffin-embedded tissues were sectioned and stained with hematoxylin and eosin (H&E) for evaluation. Trichrome staining was performed occasionally.

**RESULTS**

**Case report**

A ten-year-old, spayed, female, Staffordshire bull terrier was presented with a mass on the right upper eyelid. The condition had been present for two years and had been growing slowly. Recently, the mass had started to hang down and obscured partially the globe. There was no previous history of ocular pathology. The dog did not receive any treatment and was not up to date with vaccination and deworming.

General physical examination was unremarkable. Neuro-ophthalmic examination did not reveal any significant abnormalities.

Ophthalmic examination of the right eye revealed a subcutaneous, clinically well-circumscribed, round eyelid mass (Figure 1). The tumor involved the nasal part of the upper eyelid, reaching the nasal canthus, but with an intact free eyelid border. Intact epidermis and intact conjunctiva covered the mass exteriorly and interiorly, respectively. The mass was firm on pal-

**Figure 1.** Mesenchymal eyelid hamartoma at the medial aspect of the right upper eyelid in a ten-year-old Staffordshire bull terrier.
Both the upper and lower lacrimal puncta and nasolacrimal canaliculi were considered patent after successful nasolacrimal flushing. No exophthalmia was noted and ocular retropulsion was normal. Mild hyperemia of the palpebral and bulbar conjunctiva was noticed.

The Schirmer tear test I values (Intervet inc., Summit, New Jersey, USA) were within normal limits at 20 and 21 mm/min, for the right (OD) and left (OS) eye, respectively.

Examination of the anterior segment of both eyes by slit lamp biomicroscopy (Kowa SL-15®; Kowa Company Ltd, Tokyo, Japan) was, apart from bilateral nuclear sclerosis, within normal limits. Indirect ophthalmoscopy (Heine Omega 1000®; Heine Instruments, Herrsching, Germany) of both eyes revealed a normal fundus. Fluorescein staining was negative.

Rebound tonometry (Tonovet; Icare, Espoo, Finland) measured the intraocular pressure to be 17 and 15 mmHg for OD and OS, respectively.

Ultrasound of the orbital region, blood analysis and thoracic radiographs were recommended but declined by the owner.

Surgical excision of the mass was performed under general anesthesia. To identify and protect the superior lacrimal canaliculus, the superior lacrimal punctum was cannulated by a monofilament suture (Prolene 2/0, Ethicon LLC, Puerto Rico, USA). The abnormal tissue was sharply separated from the skin. The eyelid margin was left intact. Because the mass was poorly delineated and well-adhered to the dorsal orbital rim, complete removal was not possible. The skin incision was closed primarily (Monosyn 5/0, B Braun, Tuttingen, Germany). The dog was discharged the same day with topical antibiotic ointment (Trafloxal®, ofloxacin, Bausch & Lomb, Brussels, Belgium) OD q8h for one week, followed by q12h for one week.

The excised mass was firm on palpation, had an irregular shape and measured 2.4 cm by 1.8 cm. Macroscopically, the mass had a red-white external surface with a necrotic center on section (Figure 2). The mass was fixed in 10% buffered formalin and sections were stained with H&E and Masson’s Trichrome.
Hamartomas are disorganized and excessive amounts of mature tissue elements, indigenous to the site in which they arise. They grow independent of
the growth of the animal and hence may enlarge later in life and become a problem (Ginn et al., 2007). A hamartoma should be differentiated from a choristoma, which refers to microscopically normal cells or tissue present in an abnormal location (Kumar et al., 2013).

Although some authors describe hamartoma as a congenital lesion, this criterion is not consistently used in every definition of hamartoma (Ginn et al., 2007). In human medicine, most hamartomas are described in newborns or infants. However, eyelid hamartomas have been described in adults without history of congenital abnormality (Harris et al., 2008; Jakobiec et al., 2012). All dogs in the present case series were middle-aged to older dogs. The 10-year-old Staffordshire bull terrier in the present case report was slightly older than the dogs in the retrospective study (mean age of 8.7 years). However, the slowly growing mass had been present for two years. The hamartomatous lesions could have been subclinical, small lesions presented from birth or young age; however, this was not suggested by the clinical history.

No systemic clinical signs were reported in any of the cases. In human medicine, eyelid hamartomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Breed</th>
<th>Age (years)</th>
<th>Sex</th>
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<th>Duration (months)</th>
<th>Clinical appearance</th>
<th>Location</th>
<th>Histological findings</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Giant Schnauzer</td>
<td>7</td>
<td>MC</td>
<td>OS</td>
<td>4</td>
<td>Subconjunctival mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose, skeletal muscle tissue</td>
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<td>2</td>
<td>English Cocker spaniel</td>
<td>7</td>
<td>FS</td>
<td>OD</td>
<td>4</td>
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<td>Lateral canthus</td>
<td>Connective, adipose, skeletal muscle tissue</td>
</tr>
<tr>
<td>3</td>
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<td>6</td>
<td>M</td>
<td>OD</td>
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<td>Lateral canthus</td>
<td>Connective, adipose, skeletal muscle, peripheral nerve tissue</td>
</tr>
<tr>
<td>4</td>
<td>Golden retriever</td>
<td>7</td>
<td>MC</td>
<td>OD</td>
<td>6</td>
<td>Subconjunctival mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose tissue</td>
</tr>
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<td>5</td>
<td>Golden retriever</td>
<td>9</td>
<td>F</td>
<td>OS</td>
<td>NFS</td>
<td>Subcutaneous mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose, skeletal muscle tissue</td>
</tr>
<tr>
<td>6</td>
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<td>10</td>
<td>MC</td>
<td>OS</td>
<td>2</td>
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<td>Central eyelid</td>
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<tr>
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<td>German shepherd dog</td>
<td>10</td>
<td>FS</td>
<td>NFS</td>
<td>24</td>
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<td>Lateral canthus</td>
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<td>Doberman pinscher</td>
<td>11</td>
<td>MC</td>
<td>OD</td>
<td>NFS</td>
<td>Subcutaneous mass</td>
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<td>Connective, adipose tissue (biopsy)</td>
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<td>OS</td>
<td>NFS</td>
<td>NFS</td>
<td>Eyelid, location nfs</td>
<td>Connective, adipose tissue</td>
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<td>MC</td>
<td>OS</td>
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<td>Ventrolateral canthus</td>
<td>Connective, adipose tissue</td>
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<tr>
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<td>MC</td>
<td>OD</td>
<td>24</td>
<td>Subconjunctival mass</td>
<td>Dorsolateral canthus</td>
<td>Connective, adipose tissue</td>
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<td>OD</td>
<td>1</td>
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<td>Ventral orbit</td>
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<tr>
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<td>MC</td>
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<td>Dorsomedial canthus</td>
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<td>Dorsal conjunctiva</td>
<td>Connective, adipose, skeletal muscle tissue, cartilaginous differentiation</td>
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<tr>
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<td>14</td>
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<td>OD</td>
<td>NFS</td>
<td>Subcutaneous mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose tissue</td>
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<tr>
<td>16</td>
<td>Boxer</td>
<td>12</td>
<td>FS</td>
<td>OS</td>
<td>2</td>
<td>Orbital mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose, smooth muscle tissue</td>
</tr>
<tr>
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<td>Labrador retriever</td>
<td>10</td>
<td>MC</td>
<td>OD</td>
<td>NFS</td>
<td>Subcutaneous mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose, smooth muscle tissue</td>
</tr>
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<td>18</td>
<td>Munsterlander</td>
<td>10</td>
<td>MC</td>
<td>OD</td>
<td>2</td>
<td>Subconjunctival mass</td>
<td>Ventrolateral canthus</td>
<td>Connective, adipose, skeletal muscle tissue</td>
</tr>
<tr>
<td>19</td>
<td>Staffordshire bull terrier</td>
<td>10</td>
<td>FS</td>
<td>OD</td>
<td>24</td>
<td>Subcutaneous mass</td>
<td>Dorsomedial canthus</td>
<td>Connective, adipose, skeletal muscle, occasional nerves</td>
</tr>
<tr>
<td>20</td>
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<td>6</td>
<td>FS</td>
<td>NFS</td>
<td>3</td>
<td>Orbital mass</td>
<td>Lateral canthus</td>
<td>Connective, adipose tissue</td>
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<tr>
<td>21</td>
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<td>10</td>
<td>FS</td>
<td>OS</td>
<td>8</td>
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<td>Ventrolateral canthus</td>
<td>Connective, adipose tissue, marked cartilaginous component</td>
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<tr>
<td>22</td>
<td>Basset hound</td>
<td>11</td>
<td>FS</td>
<td>OD</td>
<td>1</td>
<td>Subcutaneous mass</td>
<td>NFS</td>
<td>Connective, adipose, muscle tissue</td>
</tr>
</tbody>
</table>

MC: male castrated; M: male; FS: female spayed; F: female; NFS: not further specified; OD: right eye; OS: left eye
have been described as part of the following clinical syndromes: Haberland, Proteus, Cowden and Birt-Hogg-Dubé (BHD) syndrome (Bardenstein et al., 1988; Lessner and Margo, 1991; Fontcuberta et al., 2011; Koti et al., 2013). Haberland syndrome or encephalocriocutaneous lipomatosis is characterized by the presence of central nervous system, ocular and cutaneous anomalies, including lipomatous hamartomas of the eyelids (Kodsi et al., 1994; Rubegni et al., 2003; Koti et al., 2013). Cowden or multiple hamartoma syndrome presents with multiple distinctive cutaneous tumor-like growths and an increased risk of breast, endometrial and thyroid carcinoma (McLean and Haynes, 1993). BHD syndrome is characterized by hamartomas of the hair follicle called fibrofolliculomas and an increased risk for spontaneous pneumothorax, lung cysts and renal neoplasia (Czyzyk-Krzeska and McCormack, 2013). Basaloid follicular hamartoma may be associated with alopecia and autoimmune diseases, such as myasthenia gravis or systemic lupus erythematosus (Ridley and Smith, 1981; Morton et al., 1998). Recently, a conjunctival hamartoma with eosinophilia has been described as a novel lesion in a child with phatase and tensin homologue (PTEN) hamartoma syndrome (Mudhar and Rogers, 2013).

In contrast to human medicine, none of these syndromes have been described in association with eyelid hamartomas in veterinary medicine. Although multifocal renal cystadenocarcinoma with nodular dermatofibrosis (RCND) in the German shepherd dog and BHD syndrome in humans are quite similar, they are not identical. The hamartomatous fibrofolliculomas described in BHD do not present in RCND-affected dogs (Lingaas et al., 2003). The presence of two hamartomatous colorectal lesions in a five-month-old Great Dane puppy with PTEN mutation showed similarities to the in human medicine described Cowden syndrome (Bemelmans et al., 2011).

None of the dogs of the retrospective study presented with more than one lesion. However, case 7 presented with a mass that recurred twice. Multiple hamartoma syndrome characterized by the presence of several hamartomas has been sparsely described in dogs (Callan et al., 2005; Taney et al., 2005; Bemelmans et al., 2011; Chanoit et al., 2012). Reported cases include a twelve-year-old dog with bilateral periodontal hamartomas (Taney et al., 2005), a six-year-old Siberian husky-mix dog with a vascular hamartoma in the pulmonary artery and bladder (Chanoit et al., 2012), and colorectal hamartomatous polyps in a five-month-old Great Dane (Bemelmans et al., 2011). Multiple epidermal hamartomas have been described in a dog following chronic immunosuppressive therapy with prednisone and cyclosporine (Callan et al., 2005).

The differential diagnosis for the nodular subcutaneous eyelid mass in the Staffordshire bull terrier included an intradermal epithelial cyst, histiocytoma, mastocytoma, lipoma, lymphoma and optic nerve sheath tumor. Because a cyst could not be excluded, no fine needle aspiration was realized in order not to complicate later surgical excision.

A predisposition of mesenchymal hamartoma of the eyelid for the lateral canthus has been reported (Kafarnik et al., 2010). Remarkably, the hamartoma described in the case report was located in the dorso-medial eyelid. The majority of the mesenchymal hamartomas reported in the retrospective study occurred near the lateral canthus. Although less frequently, lesions elsewhere on the eyelids or in the orbit were also identified.

Although the mass was clinically well-delineated in the present case report, a tight adhesion to the dorsal orbital rim was observed during surgical excision, and impeded complete resection. Analogously, a tight adhesion to the lateral palpebral ligament and/or orbital ligament was reported in more than a third of the patients of the retrospective study. Adherence of a smooth muscle hamartoma of the conjunctival fornix to the inferior border of tarsus and to the tarsal conjunctiva was described when surgical excision was performed in a two-year-old boy (Roper et al., 1999).

The histological appearance of the lesions reported here shows similarities to rhabdomyomatous mesenchymal hamartoma (RMH) described in the human literature. RMH is a rare congenital lesion of the dermis and soft tissues, consisting of a mixture of mature adipose tissue, skeletal muscle, adnexal elements and sometimes blood vessels and nerves. This entity exists under various names including striated muscle hamartoma, congenital midline hamartoma and hamartoma of cutaneous adnexa en mesenchyme (Rosenberg et al., 2002). RMH presents clinically as a subcutaneous lesion that can be located on the eyelids (Read et al., 2001). In a recent report, a mesenchymal hamartoma with rhabdomyomatous features in the orbit of a two-year-old boy has been described (Mavrikakis et al., 2007). While the exact etiology of RMH is unknown, possible explanations include aberrancy in the embryonic migration of mesodermally derived tissues or a genetic defect predisposing to the formation of hamartomas (Rosenberg et al., 2002).

In two dogs, cartilage was identified on histology. This is the first description of the presence of cartilage in pericocular mesenchymal hamartomas in dogs. Cartilaginous nodules have been reported in a primary chondromesenchymal hamartoma of the orbit in a fourteen-year-old girl (Gündüz et al., 2009). Although bone formation has been described in mesenchymal hamartomas in human medicine (Abel et al., 2004; Gündüz et al., 2009), no bone differentiation was identified in any of the current cases.

Since the fully differentiated nature of the highly collagenous connective tissue and small areas of adipose tissue is typical of mesenchymal hamartoma, it was often difficult to define the margin of the tissue sampled.

Although mesenchymal hamartomas have a benign histological appearance, malignant transformation of nasal chondromesenchymal hamartoma (Li et al.,
REFERENCES


