CASE REPORT

Calvarial hyperostosis presenting as unilateral exophthalmos in a female English Springer Spaniel

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Abstract

A 4-month-old intact female English Springer Spaniel presented to the University of Georgia Veterinary Teaching Hospital for evaluation of unilateral, progressive exophthalmos oculus sinister (OS) of 2 weeks' duration. Complete ophthalmic examination revealed moderate OS exophthalmos and lateral globe deviation. No other abnormalities were noted on physical or ophthalmic examination, ocular ultrasound, complete bloodwork, or thoracic radiography. Skull computed tomography (CT) revealed a large, focal, smoothly irregular, cavitated, expansile bony lesion involving the left caudal maxillary and left frontal bones. Biopsies, obtained through a frontal sinusotomy approach to preserve the left globe integrity, demonstrated normal reactive trabecular bone with locally extensive fibrosis. Calvarial hyperostosis was diagnosed based upon appearance on imaging, lesion unilaterality, absence of mandibular involvement, and histopathology. Six months after initial presentation, skull CT was repeated and marked reduction in the degree of frontal bone thickening was demonstrated with complete resolution of cavitations. There was marked clinical improvement with mild, nonpainful exophthalmos, and lateral globe deviation OS on ophthalmic examination. Eleven months after initial presentation, there was complete resolution of the frontal bone lesion with mild thickening of the left calvarial bones on repeat skull CT. There was no exophthalmos or globe deviation present on clinical ophthalmic examination. The proliferative osteopathic lesion was self-resolving with resolution of the exophthalmos and has not recurred to date. To the authors' knowledge, this is the first report of calvarial hyperostosis in a previously unreported breed presenting as unilateral exophthalmos.

Key Words: calvarial hyperostosis, exophthalmos, frontal sinusotomy, orbit

INTRODUCTION

Calvarial hyperostosis syndrome (CHS) is a recently described unique osteopathy characterized by a non-neoplastic, proliferative, osseous lesion of the flat bones of the skull.[1] CHS shares clinical and histologic similarities with craniomandibular osteopathy (CMO)[2] and human infantile cortical hyperostosis (ICH);[3] however, there are several distinctive features of CHS. CHS presents as a focal osteopathy, often unilateral, with a predilection of the flat bones of the skull,[1,4] while CMO and ICH are bilateral and may affect the appendicular skeleton.[2,3,5,6] CMO predominantly affects the mandible bilaterally[7,8] and has been reported in many breeds including the West Highland White Terrier,[7] Labrador,[9] Boxer,[10] Doberman Pinscher,[11] Shetland Sheepdog,[8] Great Dane,[12] Great Pyrenean Mountain Dog,[13] Akita,[5] and English Bulldog.[14] A genetic basis for CMO and ICH has been suggested.[3,7] Unlike CMO and ICH, CHS does not affect the mandible and has previously only been described in young Bull Mastiff dogs, most commonly in males.[1,4,15] It is not known whether CHS has a genetic basis, even though it has only been reported in one breed.[1]

The canine orbit is incomplete and bordered by the frontal, lacrimal, and zygomatic bones.[16] Osteomyelitis[17] and neoplasia[18] of these orbital bones may cause exophthalmos,

although this is uncommonly reported.[19] Other reported causes of exophthalmos include neoplasia of epithelial, connective tissue or hemolymphatic origin,[19–27] arteriovenous fistulation,[28] orbital varix,[29,30] cellulitis,[31,32] zygomatic sialoceles,[23,33] orbital foreign bodies[34] and inflammatory processes.[35] Exophthalmos has not been previously reported with CHS.[1,4]

This report describes a young female English Springer Spaniel affected with CHS presenting with unilateral exophthalmos. To the authors' knowledge, this is the first report of calvarial hyperostosis in a previously unreported breed presenting as unilateral exophthalmos. The proliferative osteopathic lesion was self-resolving with concurrent resolution of the exophthalmos and has not recurred to date.

CLINICAL REPORT

History, physical and ophthalmic examination, and initial diagnostics

A 4-month-old intact female English Springer Spaniel presented to the University of Georgia Veterinary Teaching Hospital (UGAVTH) for evaluation of progressive exophthalmos OS with a duration of 2 weeks. The owners reported concurrent intermittent favoring of the left side of the face and mild periodic OS blepharospasm when touched on the face. The patient had been placed on neomycin–polymyxin–dexamethasone ophthalmic ointment (Neopolydex; Falcon Pharmaceuticals, Fort Worth, TX, USA) topically OS every 8 h by the referring veterinarian 2 weeks prior to presentation with no reported improvement in the exophthalmia. A series of vaccinations given prior to presentation included three canine distemper/adenovirus type-2/leptospirosis/parainfluenza/parvovirus vaccines given 2–3 weeks apart (Recombitek; Merial, Duluth, GA, USA) and a rabies vaccination (Imrab 1; Merial, Duluth, GA, USA). Monthly heartworm (Interceptor; Novartis, New York, NY, USA) and flea (Advantix K9; Bayer, Shawnee Mission, KS, USA) prevention was administered according to the manufacturer's recommendations.

The patient had a clinically normal body weight (BCS 5/9), rectal temperature (38.4 °C), respiration rate (40 bpm), and femoral pulse rate (128 bpm) upon presentation. All other findings on physical examination were unremarkable. A complete ophthalmic examination was performed by slit-lamp biomicroscopy (Kowa SL-15; Kowa Optimed, Torrance, CA, USA) and indirect ophthalmoscopy (Keeler Vantage Plus; Dan Scott and Associates, Westerville, OH, USA). The left globe was moderately exophthalmic with lateral deviation (Fig. 1). Mild chemosis and moderate conjunctival hyperemia were present OS and interpreted to be secondary to the exophthalmos and globe deviation. Digital palpation of the left globe through closed eyelids revealed nonpainful decreased retropulsion. The patient resented deep digital palpation of the periorbital tissue caudal to the left globe and would vocalize. There were

Figure 1. The patient (female English Springer Spaniel) is depicted at the time of presentation (4 months old) to the UGAVTH with moderate OS exophthalmos and lateral globe deviation.

no other abnormalities upon examination or palpation of the mandible, periorbital soft-tissue structures, dorsal skull, or oral cavity. Both oculus dexter (OD) and OS were clinically normal on complete ophthalmic examination with normal ocular motility oculus unistas (OU), a Schirmer tear test value of 20 mm/min OU (Schirmer Tear Test; Merck and Company, Inc., Whitehouse Station, NJ, USA) and an intraocular pressure of 17 mmHg OD and 14 mmHg OS measured with applanation tonometry (Tonopen XL; Reichert Technologies, Depew, NY, USA). There was no corneal or conjunctival fluorescein stain retention OU.

Differential diagnoses for the exophthalmos included orbital cellulitis or abscess,[32,36] orbital foreign body,[34] other inflammatory process or pseudotumor,[35] osteomyelitis,[17] vascular anomaly,[28,29] salivary mucocele,[33] and neoplasia.[18,19,24] Complete blood count and blood chemistry were within hematologically normal limits considering the patient's age. Thoracic radiographs and ocular ultrasound were unremarkable. The patient was admitted to the UGAVTH, and CT of the skull was scheduled for the following day.

Initial CT examination and CT-guided biopsy

The patient was premedicated prior to general anesthesia with acepromazine (0.02 mg/kg IV; Fort Dodge, Fort Dodge, IO, USA), glycopyrrolate (0.005 mg/kg IV; Baxter, Deerfield, IL, USA), and hydromorphone (0.1 mg/kg IV; Baxter, Deerfield, IL, USA). Anesthetic induction was achieved with propofol (4 mg/kg IV; Propoflo, Abbott Animal Health, North Chicago, IL, USA) to effect. General anesthesia was maintained after intratracheal intubation with inhalant isoflurane 1–2% in oxygen (Isoflo; Abbott Animal Health, North Chicago, IL, USA).

Helical CT (HiSpeed NX/i Dual Slice; General Electric, Atlanta, GA, USA) of the head was performed from the level of the nasal planum to the temporomandibular joints. Images were obtained prior to and following the intravenous
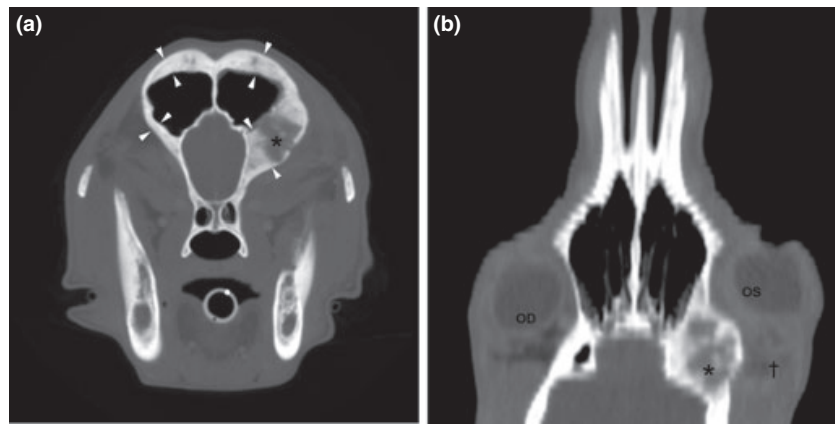
Figure 2. A representative computed tomography transverse plane image with bone algorithm and windowing at the level of the rostral frontal cerebral lobes (a) and dorsal plane reconstruction image with soft-tissue algorithm and windowing at the level of the globes (b) of the patient (4-month-old female Springer Spaniel) at initial presentation are depicted. On the transverse plane image (a), a large, focal, smoothly irregular, cavitated, expansile bony lesion characterized by a central soft-tissue attenuating area surrounded by smoothly irregular bone with some ill-defined and discontinuous osseous margins is present in the ventrolateral aspect of the frontal bone (asterisk). Focally extensive bilateral heterogenous thickening of the frontal bones surrounding the sinuses (arrowheads) is noted. On the dorsal plane reconstructed image (b), the left globe OS is laterally displaced with moderate exophthalmos. The left retrobulbar tissues are asymmetrically thickened and moderately contrast enhanced (dagger) secondary to the large bony lesion (asterisk), showing marked disparity between the unaffected right side (OD: oculus dexter).

administration of 28.5 mL of Iohexol 350 mg/mL (Omnipaque 350; GE Healthcare, Piscataway, NJ, USA). Transverse images were reconstructed in 2-mm slices with bone and soft-tissue algorithms. Sagittal and dorsal plane reformations were also made. A large, expansile, heterogeneously mineralized lesion was present involving the left caudal maxillary and frontal bones. A central soft-tissue attenuating area (Houndsfield units: approximately 37) was located in the ventrolateral aspect of the left frontal bone and was surrounded by smoothly irregular bone with some ill-defined and discontinuous osseous margins (Fig. 2). Following iodinated contrast administration, there was uniform moderate enhancement in the soft-tissue attenuating region (Houndsfield units: approximately 122), indicating the presence of vascularized tissue. There were multiple small mineral foci within the central soft-tissue focus and at the lateral aspect of the mass. Soft-tissue attenuating regions were present at the rostral aspect of the mass. The frontal bone was bilaterally thickened with subjectively increased mineral in the diploe that extended rostrally to the cribriform plate and caudally to the extent of included anatomy in the CT examination (Fig. 2a). Extension into the cranial vault or nasal cavity was not present. Mild contrast enhancement was present in the left periorbital soft tissues interpreted to be inflammation secondary to tissue compression and displacement from the expansile, bony mass. The osseous proliferation and retrobulbar thickened soft tissue contacted the caudomedial margin of the globe, and rostral and lateral deviation of the globe was seen on transverse and dorsal plane images (Fig. 2b).

Multiple fine-needle aspirates, Jamshidi biopsies (Jamshidi needle; CareFusion Corporation, San Diego, CA, USA), and microbial culture sampling were performed using CT guidance for optimal needle placement as previously described.[37,38] The mineral and soft-tissue attenuating regions were both sampled for full characterization of the lesion. The patient was recovered from anesthesia routinely, placed on carprofen (2.2 mg/kg PO Q12 h for 3 days; Rimadyl, Pfizer, New York, NY, USA) and topical ophthalmic neomycin–polymyxin–dexamethasone (Q8 h until recheck; Neopolydex suspension, Falcon Pharmaceuticals, Fort Worth, TX, USA) OS, and discharged pending biopsy results.

Histopathologic examination of the biopsy sections revealed bony trabeculae and mineralized woven and lamellar bone lined by plump osteoblasts and separated by loose fibrous connective tissue stroma and more densely cellular regions of fibroblasts (Fig. 3a). These changes were interpreted as fibrous and bony proliferation. Osteomyelitis or neoplasia could not be ruled out. Because a specific diagnosis was difficult because of the small amount of material present, the recommendation was made to obtain larger biopsy samples. Aerobic and anaerobic culture did not yield any bacterial growth.

Biopsy and frontal sinusotomy

The patient was positioned in sternal recumbency and aseptically prepared and draped for surgery. A skin incision was made on the midline of the skull in the region of the frontal bone extending rostrally to the level of the medial canthi and caudally to the caudal extent of the frontal bone. Soft tissue was bluntly dissected to expose the frontal bone. A Jacob's chuck with a Steinmann pin was used to penetrate the bone over the left frontal sinus. An oscillating saw was used to make a 1.5 cm × 1.5 cm opening over the frontal sinus. Bone samples were taken from the left ventral and lateral aspects of the
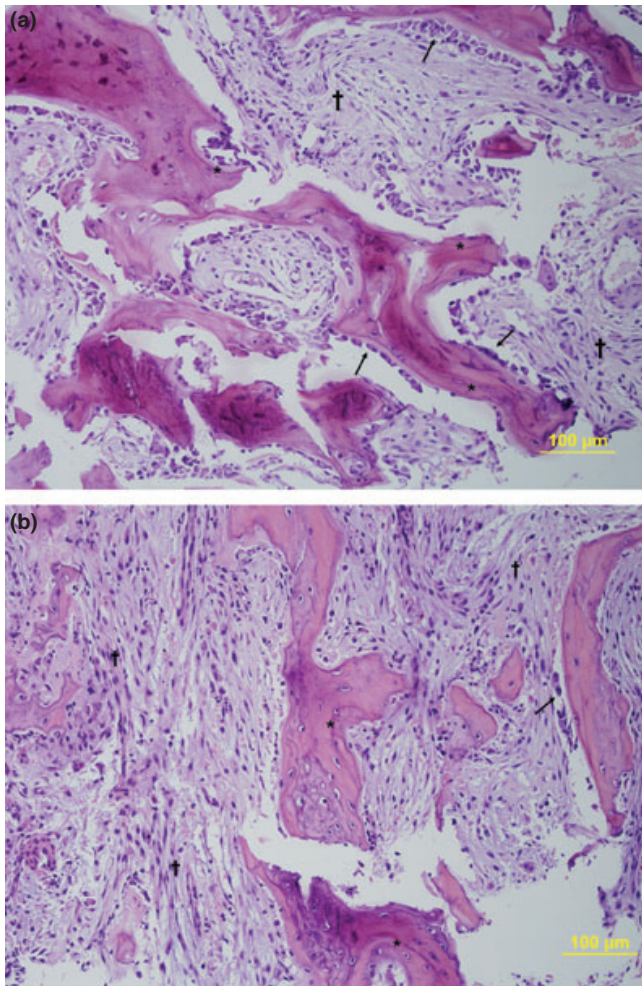
Figure 3. Photomicrographs (20× magnification) of a representative biopsy sample taken with computed tomography guidance (a) and a representative biopsy sample taken via a frontal sinusotomy approach (b) from the patient (4-month-old female Springer Spaniel) are depicted. There are bony trabeculae present with slightly basophilic remodeling lines running parallel to the edges (asterisks) lined by plump osteoblasts (arrows) consistent with reactive bone. The trabeculae are separated by loose fibrous connective tissue with multifocally moderately dense regions of fibroblasts (daggers).

frontal sinus. The bone was submitted for histopathologic examination. Hemostasis was achieved with electrocautery and cold saline lavage. The frontal sinus was irrigated prior to closure. The periosteum, subcutaneous tissue, and skin were closed routinely.[39] The patient was recovered and discharged with the same instructions for medication administration as after CT biopsies, with recommendations for skin suture removal by the referring veterinarian in 10–14 days.

Histopathologic examination of the biopsy samples revealed bony trabeculae with multiple slightly basophilic lines running parallel to the edges (remodeling lines). There was multifocal increased fibrosis surrounding the bony spicules and moderate numbers of osteoblasts lining the bony fragments multifocally (Fig. 3b). These changes were consistent with reactive bone and locally extensive fibrosis. There

Figure 4. The patient (female English Springer Spaniel) is shown 6 months after initial presentation. There is mild OS exophthalmos and lateral globe deviation present; however, there is marked resolution as compared to initial presentation (Fig. 1).

was no evidence of neoplasia or osteomyelitis. Based on the CT appearance and histopathology, calvarial hyperostosis was diagnosed and the recommendation was made for a follow-up CT examination in 6 months with discontinuation of topical and oral medications. The owners were advised to rigorously observe the patient for any worsening of OS exophthalmos or discomfort and contact the UGAVTH for further evaluation if noted. A telephone conversation 2 weeks after discharge revealed no change to the patient's status.

Six-month ophthalmic and CT examination
Six months after initial presentation, the patient presented to the UGAVTH for re-evaluation. The owners reported marked resolution of OS exophthalmos gradually over the subsequent 3 months following discharge. Marked clinical improvement was noted on full ophthalmic examination; however, the left globe was mildly exophthalmic and laterally displaced (Fig. 4). Retropulsion was slightly decreased in the left eye and nonpainful. Deep digital palpation of periorbital soft tissue was nonpainful. There were no abnormalities in the remaining ophthalmic or physical examination. The patient had undergone ovariohysterectomy by the referring veterinarian since the last visit to U-GAVTH. There were no other changes to the monthly heartworm and flea prevention schedule, and no other topical or systemic medications had been given.

A repeat CT examination was performed under general anesthesia using the same anesthetic protocol and contrast administration as with the initial CT. The majority of the frontal bones were of normal thickness, and the diploes had a better defined trabecular pattern with less mineral attenuation compared with that noted previously (Fig. 5). A small area of thickening remained at the ventral aspect of the rostral frontal bone. The bone in this area had uniform mineral attenuation with complete resolution of cavitations. By comparison to the prior examination, this correlated with marked resolution of the previous lesion.
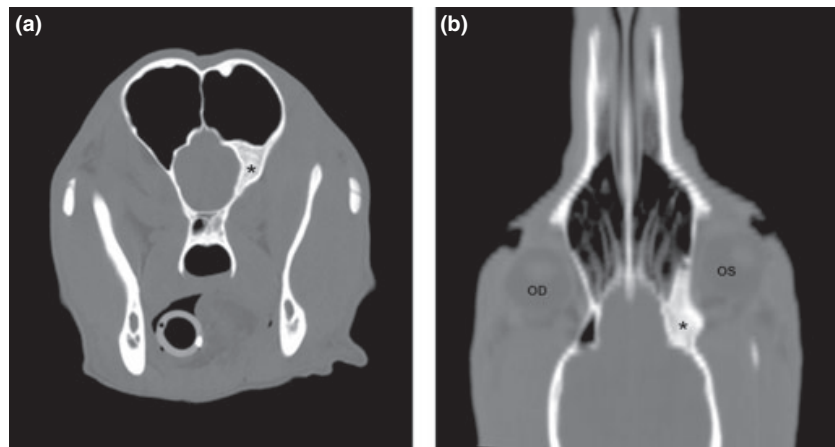
Figure 5. A representative computed tomography transverse plane image with bone algorithm and windowing at the level of the rostral frontal cerebral lobes (a) and dorsal plane reconstruction image with soft-tissue algorithm and windowing at the level of the globes (b) of the patient (female Springer Spaniel) 6 months after initial presentation are depicted. On the transverse plane image (a) and dorsal plane image (b), focal thickening of the left frontal bone with uniform mineralization (asterisk) is present. When compared with initial presentation, there is marked resolution of the lesion with absence of cavitations and central soft-tissue core attenuation noted at that time (Fig. 2). The previously noted diffuse heterogenous bilateral thickening of the frontal bones surrounding the sinuses has completely resolved. On the dorsal plane reconstructed image (b), the left globe OS is mildly laterally displaced with mild exophthalmos. The left retrobulbar tissues have good symmetry with the unaffected right side (OD: oculus dexter) and do not contrast enhance.

Figure 6. The patient (female English Springer Spaniel) is shown eleven months after initial presentation. There is no exophthalmos or lateral globe deviation present. The patient is clinically normal with facial symmetry.

The patient was discharged after recovery from anesthesia, and the recommendation was made to continue at-home observation and return in 6 months for CT at developmental maturity.

Eleven-month ophthalmic and CT examination
The patient represented to the UGAVTH for evaluation eleven months after initial presentation. The left globe was in a clinically normal position with complete resolution of the previous exophthalmos and lateral globe deviation (Fig. 6). Retropulsion was clinically normal, and deep digital palpation of periorbital soft tissue continued to be nonpainful. There were no abnormalities in the remaining ophthalmic or physical examination.

A CT examination was performed under general anesthesia as previously described. The focal area of thickening in the ventral aspect of the left frontal bone was mildly reduced compared with the exam 5 months prior. The orbit was unchanged in dimension, and the eye was subjectively similarly positioned in the orbit as compared to the right eye (Fig. 7).

The patient was discharged, and at the time of this writing, the patient remains clinically normal.

DISCUSSION

The case herein describes calvarial hyperostosis syndrome in a female English Springer Spaniel presenting as unilateral exophthalmos. Canine osteoproliferative lesions of the flat bones of the skull tend to be self-limiting and occur in young, large breed dogs.[1,2,8] CHS, in particular, has only been reported in young Bull Mastiff dogs, with males more commonly affected.[1,4,15] A young male Pit Bull Terrrier with bilateral calvarial flat bone thickening has been described with bilateral mandibular involvement along with other flat bones of the skull.[40] The authors of this report challenged the difference in CMO and CHS and suggest that these clinical entities may be the same. It is beyond the scope of our paper to discuss this contention. While similarities exist between these clinical entities, there are distinct differences in CMO and CHS, namely the presence of a focal lesions, lesion unilaterality, and absence of mandibular involvement with CHS.[1,2,4] Based on the presence of bilateral mandibular involvement in the aforementioned Pit Bull Terrier, a diagnosis of craniomandibular osteopathy would seem appropriate. Lesion unilaterality is a unique feature of CHS, although bilateral calvarial
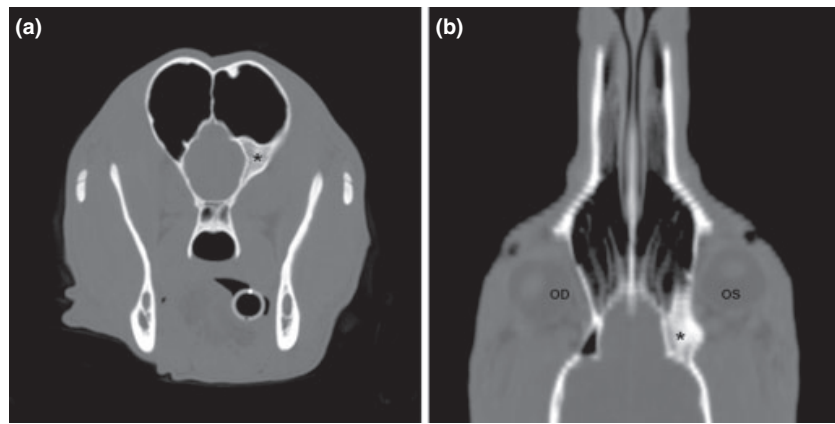
Figure 7. A representative computed tomography (CT) transverse plane image with bone algorithm and windowing at the level of the rostral frontal cerebral lobes (a) and dorsal plane reconstruction image with soft-tissue algorithm and windowing at the level of the globes (b) of the patient (female Springer Spaniel) eleven months after initial presentation are depicted. On the transverse plane image (a) and dorsal plane image (b), focal thickening of the left frontal bone with uniform mineralization (asterisk) is present. This is decreased as compared to the 6-month CT evaluation (Fig. 5). On the dorsal plane reconstructed image (b), the left globe (OS) is a normal position within the orbit and there is symmetry with the unaffected right side (OD: oculus dexter).

bone thickening may occur concurrently.[1,4] As has been previously described for CHS, the lesion described in our report was focally extensive and unilateral with concurrent frontal bone thickening bilaterally (Fig. 2a). Additionally, this lesion did not involve the mandible, further differentiating it as CHS. While our case describes CHS affecting a young, large breed dog, consistent with other reports, it is unique in that the patient affected was a breed other than a Bull Mastiff. This would suggest that CHS may occur in other breeds.

This case was also unique in that the primary presenting complaint was that of unilateral exophthalmos. To the authors' knowledge, CHS has not been documented as a cause of the exophthalmos. It is not surprising; however, that exophthalmos may occur with CHS as skull bones comprise the bony portion of the orbit. The expansile lesion reported here primarily affected the frontal bone, which comprises the majority of the canine medial orbital wall, thus causing exophthalmos and lateral globe deviation. The lesion resolved over time with subsequent resolution of the exophthalmos and discomfort.

All cases of CHS previously reported have been associated with pain on palpation of the lesion. Supportive care is recommended as the lesion tends to be self-limiting.[1] Because this patient's lesion was located in the medial orbit, it is difficult to determine whether it was painful. The patient did have pain on deep palpation of periorbital soft-tissue caudal to the globe at the time of presentation. It cannot be determined whether the discomfort was because of mild inflammation of soft tissue secondary to displacement from the expansile mass or primary pain related to the bony mass. The owner reported intermittent 'favoring' the left side of the patient's face when touched at home prior to initial presentation. The lack of pain on retropulsion would suggest that the discomfort was related to the mass directly. The owners did not notice reluctance to eat

or play at any time, nor did they report an improvement in the patient's behavior when carprofen was administered. Carprofen was thus administered only in the immediate postoperative periods after biopsies were taken. Neopolydex was used intermittently for a short period of time to help decrease periocular inflammation. This was subsequently discontinued with clinical resolution of the hyperemia and chemosis.

CT was used as the imaging modality of choice in our case as it provides superior visualization of the periorbital structures.[41,42] Skull radiographs are often not of diagnostic value in cases of orbital disease and, for this reason, were not considered for this patient.[24,43,44] Although MRI may have been considered,[34,39,45–48] CT was chosen in this case to facilitate biopsies, determine whether there was bone involvement and define the extent of the lesion. In addition, at our facility, CT examination is approximately half the cost of MRI, and the possibility of repeat imaging was considered likely in view of the patient's age. On subsequent follow-up examinations, CT was the imaging modality of choice in our patient as the lesion was bony.

This case describes a frontal sinusotomy approach for biopsy of the medial orbital wall. Biopsy sampling via a lateral,[49] modified lateral,[50,51] or transfrontal[52] orbitotomy was considered; however, these approaches would likely not result in adequate exposure for sampling as the lesion was located in the centromedial aspect of the left orbit in the frontal and maxillary bones. Orbital exenteration[53–55] with lesion debulking and sampling was also considered as omyelitis and neoplasia were differential diagnoses with possible systemic or life-threatening implications. The loss of OS made this option unacceptable. Therefore, the recommendation was made to obtain larger samples via a frontal sinusotomy approach.[56] A medial orbitotomy was not performed as the lesion was large, and adequate samples were obtained without entry into the orbit. It is plausible that the medial

orbit could be accessed through this approach if CT was performed prior to delineate landmarks. In our case, CT was used to define the exact margins and location of the lesion and facilitate access through the frontal sinus, thus preserving globe integrity. The bone over the frontal sinus was not replaced after biopsy samples were taken. Complete remodeling of the dorsal sinus was noted on follow-up CT examination.

Calvarial hyperostosis syndrome should be considered in breeds other than the Bull Mastiff if a unilateral osteoproliferative lesion of the flat bones of the skull is present. In addition, exophthalmos may be the presenting clinical sign for CHS. A frontal sinusotomy approach to the medial orbit is globe-sparing and should be considered in select cases in which access to a particular lesion will not be attained with a lateral, modified lateral or transfrontal orbitotomy. The lesion reported here, in agreement with other cases of CHS, was self-resolving and has not recurred at the time of this writing. The presenting exophthalmos, globe deviation, and discomfort also completely resolved, and the patient remains clinically normal.

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