Microphthalmia, corneal dermoids, and congenital anomalies resembling Goldenhar syndrome in a cat

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An 18-month-old spayed female domestic shorthair cat was referred to the Comparative Ophthalmology Service of the Veterinary Teaching Hospital at Michigan State University for evaluation of ocular abnormalities. The cat had been found outdoors and subsequently adopted as a pet at approximately 6 weeks of age. On previous examinations, there was no other pertinent medical history, vaccination status was current, and the referring veterinarian noted a body condition score of 5 when evaluating young cats with similar clinical signs. (J Am Vet Med Assoc 2018;252:324–329)

CASE DESCRIPTION
An 18-month-old spayed female domestic shorthair cat was evaluated because of conjunctivitis and skin-fold dermatitis secondary to bilateral microphthalmia, corneal dermoids, and ankyloblepharon.

CLINICAL FINDINGS
Physical examination revealed bilateral microphthalmia, bilaterally symmetrical corneal dermoids, ankyloblepharon, superior and inferior entropion, prognathism, and facial asymmetry with deviation of the nasal septum. Computed tomography revealed malformed, thickened bony orbits with mineralization of the orbital ligament bilaterally. Moderate rightward deviation of the nasal septum and ventral nasal meatus was also evident, with no identifiable maxillary sinuses. Results of MRI of the brain were unremarkable. Abdominal ultrasonography showed an irregularly marginated left kidney and a right kidney defect suggestive of chronic renal infarction. An abnormal, well-demarcated, focally thickened region of the muscularis externa of the jejunum was also evident.

TREATMENT AND OUTCOME
Transpalpebral enucleation was performed bilaterally. Histologic examination of ocular tissues confirmed the corneal dermoids and microphthalmia with anterior and posterior segment dysgenesis and cataracts in both eyes. Ocular discomfort resolved after postoperative recovery, and follow-up revealed that the patient’s activity level and quality of life were excellent. No clinical signs of upper respiratory, urinary, or gastrointestinal tract disease were observed during the approximately 3.5-year follow-up period.

CLINICAL RELEVANCE
The congenital abnormalities observed resembled those described for human patients with Goldenhar syndrome, and the outcome of treatment was favorable. This report may prompt clinicians to consider this diagnosis when evaluating young cats with similar clinical signs. (J Am Vet Med Assoc 2018;252:324–329)

In the 6 months prior to examination, the cat had been treated by the primary care veterinarian for recurrent skin fold pyoderma and *Malassezia* dermatitis of the perirectal skin adjacent to the dermoids bilaterally. Each episode promptly resolved with empirical administration of amoxicillin-clavulanic acid (13.75 mg/kg [6.25 mg/lb], PO, q 12 h) and chlorhexidine-miconazole pledgets (containing 17.4 mg of miconazole and 20 mg of chlorhexidine gluconate and applied topically to the affected area every 12 hours). A small umbilical hernia had been repaired during elective ovariohysterectomy at 5 months of age. The cat had also been evaluated for a 10-day episode of stranguria, pollakiuria, and struvite crystalluria 3 months prior to referral, with a presumptive diagnosis of feline interstitial cystitis. The referring veterinarian noted a body condition score of 5 on a scale of 1 to 9, with results of cardiothoracic auscultation and abdominal palpation unremarkable during previous examinations. There was no other pertinent medical history, vaccination status was current, and the cat lived strictly indoors.

To address the chronic signs of discomfort associated with entropion and recurrent pyoderma, bi-
lateral transpalpebral enucleation was elected. Preoperative testing included a CBC and serum biochemical panel; all values were within reference limits. An IV catheter was placed in a cephalic vein, and general anesthesia was induced with propofol (approx 6 mg/kg [2.7 mg/lb], IV). An endotracheal tube was placed, and anesthesia was maintained with delivery of isoflurane in oxygen (at a maintenance concentration of approx 2%). The patient was positioned in dorsal recumbency. Initial palpebral apposition was achieved with 4-0 silk suture material placed in a simple continuous pattern. The skin around the palpebral fissures was elliptically incised with a No. 15 scalpel blade to the level of the tarsal plate, and the palpebral skin was undermined by means of blunt dissection with Metzenbaum scissors to the orbital rim. The periorbital fascia was transected to expose the orbital contents. The extraocular muscles were transected at the level of globe insertion, and the optic nerve was severed approximately 2 mm caudal to its insertion on the globe. Subsequently, the globe was removed en bloc. An identical procedure was performed on the contralateral eye. Both globes were submitted for histologic examination. After bilateral enucleation, the periorbital fascia and subcutaneous tissues were apposed separately with 4-0 synthetic absorbable suture material in a simple continuous pattern, and the skin incision was closed with 4-0 nylon in a simple interrupted pattern. The cat recovered from anesthesia without apparent complications. An Elizabethan collar was fitted, and buprenorphine (0.015 mg/kg [0.007 mg/lb], sublingually) was administered for postoperative analgesia. During the next 14 days, the patient’s activity was restricted and the Elizabethan collar was worn at all times.

On gross examination, both excised globes were markedly deformed and appeared small, and the right eye had a multilocular appearance (Figure 2). Histologic examination revealed dome-shaped exophytic projections of well-differentiated haired skin, adipose tissue, and interspersed skeletal muscle bundles, with scattered small aggregates of mixed inflammatory cells, adjacent to the corneal stroma of both eyes. In the left eye, neutrophils and macrophages formed focal nodular aggregates centered around free hair shafts. Similar inflammatory cells mixed with desquamated epithelial cells and multiple free hair shafts were also present within the conjunctival sac of the left eye (Figure 3). No infectious agents (including yeasts) were noted in any sections examined.

The Descemet membrane appeared intact in the examined sections of the left eye but was segmentally absent in the right eye. The cornea was continuous with a scleral sheet lined by a variably thick uveal tract. The internal lining of the left eye consisted of pigmented neuroectodermal epithelium; in the right eye, this pigmented epithelium also lined, together with an outer nonpigmented epithelial layer, multiple papillary fronds of delicate fibrovascular stroma. There was no evidence of a neurosensory layer that would indicate retinal differentiation. The lens had marked cataractous changes in both eyes and was adhered to the corneal stroma in the right eye. In the right eye, there was additionally a focal area of osseous metaplasia within the posterior aspect of the sclera, adjacent to the insertion of the optic nerve, which was gliotic. The histopathologic diagnosis was...
multiple dysplastic changes of the eyes and adnexa, including bilateral microphthalmia, corneal dermoids, cataract, and anterior and posterior segment dysgenesis. There was also focal pyogranulomatous conjunctivitis of the left eye associated with free hair shafts originating from the corneal dermoid.

Because of the facial asymmetry and palpable bony irregularities, CT of the skull was performed (Figure 4). This revealed thick and irregularly margined bony orbits bilaterally, with extensive mineralization of the left and right orbital ligaments that was subjectively greater than would typically be expected in cats. There was moderate rightward deviation of the nasal septum and the ventral nasal meatus, and neither the left nor right maxillary sinuses could be identified. As such, the bony proliferation and mineralization of the orbit and orbital ligaments in both eyes as well as the nasal cavity malformation were strongly suggestive of a congenital craniofacial anomaly. Magnetic resonance imaging was also performed, confirming the results of CT. Examination of images revealed bilaterally thickened, malformed bony orbits that contained moderate amounts of fat. There was no evidence of any brain abnormality on diagnostic imaging.

Because of the history of signs of lower urinary tract disease, transabdominal ultrasonography was also performed. Results indicated the presence of an abnormal segment of jejunum, measuring 2.5 cm in length, with a focal area of thickening of the muscularis externa (Figure 5). The intestinal wall thickness was > 0.4 cm (reference range, 0.2 to 0.3 cm). The left kidney had a mildly irregular ventral margin, and a wedge-shaped defect was noted at the caudal pole of the right kidney, consistent with chronic renal infarction. Finely granular, hyperechoic shadowing material was observed in the dependent portion of the urinary bladder, consistent with the history of crystalluria. The urinary bladder wall thickness was within reference limits. The pancreas was hyperechoic. The clinical importance of these findings was uncertain; however, the pancreatic abnormality was suspected to be unrelated to the congenital syndrome.

The cat returned for a recheck examination 14 days after surgery. At this time, the surgical wounds had healed completely, and the owners noted that the cat appeared to be in good overall health. Six-month and 1-year follow-up discussions confirmed that the cat’s overall activity level and interest in its surroundings had improved substantially following recovery from surgery, likely because of elimination of chronic entropion with a resultant improved overall quality of life. Because the cat had presumably been blind since birth, the enucleation procedure appeared to have had minimal impact on sensory function or ability to thrive. There were no clinical signs suggestive of renal, pancreatic, or gastrointestinal disease related to the abnormalities noted on abdominal ultrasonography during the follow-up period. During the most recent follow-up visit at our hospital at approximately 5 years of age, there had been no changes in overall health noted by the owners or primary care veterinarian.
Discussion

The cat described in the present report had bilateral microphthalmia, bilaterally symmetric corneal dermoids, anterior and posterior segment dysgenesis, cataract, malformed bony orbits, absence of the maxillary sinuses, prognathism, and facial asymmetry. The presence of a renal infarct and an apparent focal thickening of the jejunal muscularis externa were also of note. These abnormalities appeared to resemble a well-described condition affecting human patients referred to as Goldenhar syndrome. This is a condition characterized by multiple developmental anomalies of the face and head and also possibly affecting vertebral, cardiac, urogenital, and gastrointestinal structures.2

Microphthalmia occurs sporadically in domestic animals and is thought to occur rarely in cats.3–6 In humans, microphthalmia affects 3% to 11% of blind children, with a prevalence of approximately 19 cases/100,000 live births.7,8 Although multiple congenital ocular abnormalities associated with microphthalmia have been reported previously in cats, these have consisted primarily of persistent pupillary membranes, eyelid agenesis, and colobomas in the caudal segment of the eye.9–12 As such, results of previous reports are very different from the abnormalities in the cat described here. Whether microphthalmia occurs in the presence of other ocular and craniofacial abnormalities can help to determine the phase of prenatal development when the abnormality may have been initiated.3 In the cat of the present report, the presence of bilateral microphthalmia with concurrent ankyloblepharon and anterior and posterior segment dysgenesis was highly suggestive of defective optic vesicle formation during prenatal development. The optic vesicles arise from the optic sulci, which exist as paired evaginations of the neuroectoderm in the region of the forebrain at approximately day 13 of gestation. The optic vesicles enlarge between days 15 and 17 of gestation, until they contact the basal lamina of the surface ectoderm and thereby induce the formation of the palpebral fissures and other surrounding structures such as the orbits and periocular connective tissue.13,14 A defect during formation of the optic vesicle might therefore lead to an abnormally small globe, with a correspondingly abnormal bony orbit, orbital ligament, and palpebral fissure.3,15

The presence of bilateral corneal dermoids in the cat of the present report was suggestive of a congenital defect arising over a similar period during prenatal development. The corneal epithelium is formed from the neuroectoderm in the region of the forebrain at approximately day 13 of gestation. The optic vesicles enlarge between days 15 and 17 of gestation, until they contact the basal lamina of the surface ectoderm and thereby induce the formation of the palpebral fissures and other surrounding structures such as the orbits and periocular connective tissue.13,14 A defect during formation of the optic vesicle might therefore lead to an abnormally small globe, with a correspondingly abnormal bony orbit, orbital ligament, and palpebral fissure.3,15

The presence of bilateral corneal dermoids in the cat of the present report was suggestive of a congenital defect arising over a similar period during prenatal development. The corneal epithelium is formed from the surface ectoderm after induction by the optic vesicle.13 Thus, abnormal differentiation of cells from the surface ectoderm and neural crest can produce well-differentiated, haired skin in the corneal epithelium.3 Dermoids can occur in the palpebral conjunctiva, at the eyelid margin, or, more commonly, in the region of the temporal limbus and cornea, as for this case.5,16,17
Neural crest cells, in conjunction with the mesoderm, are also responsible for the formation of the pharyngeal arches during fetal development. The pharyngeal arches are precursors to a number of vital structures including the cranial nerves, arteries, muscles of mastication and swallowing, and bony structures of the face, ear, and mandible. Whereas deviation of the nasal septum alone may be a normal anatomic variant in some cats, the prognathism, facial asymmetry, and absence of maxillary sinuses noted in the cat of the present report suggested a developmental anomaly of the first pharyngeal arch, which ultimately develops into those structures. Interestingly, the first pharyngeal arch develops at approximately days 14 to 15 of gestation in cats. This coincides with the time when the optic vesicles form. We therefore suggest that the craniofacial anomalies in the cat of the present report all originated at the same time during prenatal development.

The abnormalities in this cat and their embryonic origins were notable because of their striking similarity to a human condition referred to as Goldenhar syndrome. We are not aware of previous reports of this syndrome in species other than humans. Goldenhar syndrome (also known as hemifacial microsomia or oculo-auriculo-vertebral syndrome depending on the accompanying symptoms) involves a developmental anomaly of the first or second branchial arches and is reportedly one of the most common congenital disorders of the face in human patients, second only to cleft lip and palate. The first and second pharyngeal arches contribute to the muscles of mastication, muscles of the face, bones of the maxilla and mandible, middle ear structures, trigeminal and facial nerves, and various arterial structures. Therefore, abnormal fetal development of the pharyngeal arches can produce a highly variable array of phenotypic aberrations involving the face and head, but which can also involve vertebral, cardiac, urogenital, and gastrointestinal structures. Human patients with Goldenhar syndrome may have epibulbar dermoids, microphthalmia, anophthalmia, colobomas of 1 or more ocular structures, cataracts, abnormal palpebral fissures, preauricular skin tags, microtia, external ear malformations, abnormal hearing, facial hypoplasia, maxillary hypoplasia, or mandibular hypoplasia. Additionally, vertebral column anomalies, cleft lip or palate, congenital heart disease, ectopic kidneys, abnormal ureteral or urethral morphology, imperforate anus, esophageal atresia, and abnormalities of the CNS have been attributed to Goldenhar syndrome. According to 1 study, Goldenhar syndrome was the most frequently reported syndrome in patients with ocular dermoids. Most patients have abnormalities that are unilateral and right-sided, with bilateral disease affecting only approximately 10% of patients. However, epibulbar dermoids are commonly a bilateral finding. The cat of the present report had bilateral microphthalmia, corneal dermoids, ankyloblepharon, absence of maxillary sinuses, and prognathia, with abnormalities suggestive of a developmental defect at the time of embryonic development of the first pharyngeal arch and optic vesicles. As such, we surmised that the congenital condition represented a feline variant of Goldenhar syndrome. The presumptive renal infarction and apparent jejunal muscularis externa abnormality may have been related, or they may have represented nonspecific findings.

Because the cat of the present report was found outdoors at 6 weeks of age, with unknown parentage and history, the underlying etiology of the congenital abnormalities could only be speculated. Hemifacial microsomia in human patients has been associated with maternal vasoactive medication use, diabetes mellitus, multiple gestations, and vaginal bleeding, suggesting vascular disruption as 1 potential cause. Similar clinical signs of disease have been produced experimentally in mice in association with a teratogen-induced hematoma of the fetal artery of the second branchial arch, producing tissue necrosis. This suggests that the disease may be related to abnormal blood flow or tissue ischemia. Chromosomal abnormalities, such as trisomy 11 and 22, and autosomal dominant familial inheritance patterns have also been suggested in human patients. An infectious etiology was considered, but common feline pathogens such as feline panleukopenia virus, herpesvirus, calcivirus, and toxoplasmosis have not been associated with the spectrum of abnormalities described. Furthermore, whereas trauma at a young age has been associated with ocular abnormalities in juvenile cats, the primary histologic findings, including corneal perforation, protrusion of the uvea, and uveal hematopoiesis, differ from those of the cat described here. Findings for the cat described in the present report should prompt careful investigation of cats examined with similar signs.

Acknowledgments

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References

Effects of weight loss with a moderate-protein, high-fiber diet on body composition, voluntary physical activity, and fecal microbiota of obese cats
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OBJECTIVE
To determine effects of restriction feeding of a moderate-protein, high-fiber diet on loss of body weight (BW), voluntary physical activity, body composition, and fecal microbiota of overweight cats.

ANIMALS
8 neutered male adult cats.

PROCEDURES
After BW maintenance for 4 weeks (week 0 = last week of baseline period), cats were fed to lose approximately 1.5% of BW/wk for 18 weeks. Food intake (daily), BW (twice per week), body condition score (weekly), body composition (every 4 weeks), serum biochemical analysis (weeks 0, 1, 2, 4, 8, 12, and 16), physical activity (every 6 weeks), and fecal microbiota (weeks 0, 1, 2, 4, 8, 12, and 16) were assessed.

RESULTS
BW, body condition score, serum triglyceride concentration, and body fat mass and percentage decreased significantly over time. Lean mass decreased significantly at weeks 12 and 16. Energy required to maintain BW was 14% less than National Research Council estimates for overweight cats and 16% more than resting energy requirement estimates. Energy required for weight loss was 11% more, 6% less, and 16% less than American Animal Hospital Association recommendations for weight loss (80% of resting energy requirement) at weeks 1 through 4, 5 through 8, and 9 through 18, respectively. Relative abundance of Actinobacteria increased and Bacteroidetes decreased with weight loss.

CONCLUSIONS AND CLINICAL RELEVANCE
Restricted feeding of a moderate-protein, high-fiber diet appeared to be a safe and effective means for weight loss in cats. Energy requirements for neutered cats may be overestimated and should be reconsidered. (Am J Vet Res 2018;79:181–190)