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CASE REPORT

Anterior segment dysgenesis (Peters' anomaly) in two snow leopard (*Panthera uncia*) cubs

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Abstract

Two sibling snow leopards, a male and a female, with bilateral anterior segment dysgenesis (ASD), are reported. Both snow leopards also had colobomas of both upper eyelids. All eyes exhibited a central corneal opacity associated with a defect in posterior corneal stroma, endothelium and Descemet's membrane. Iris strands were present attached to the termination of Descemet's membrane and to the periphery of the posterior corneal defect. The iris was hypoplastic, and cataract was present in all four eyes. The left eye of the female was microphthalmic, with no trabecular meshwork and with persistent remnant of the hyaloid artery. The male had hydrocephalus and thus some of the features of Peters' plus syndrome (Peters' anomaly in addition to systemic malformations). The histological findings in the eyes of these snow leopard siblings are identical with those described in humans with Peters' anomaly.

Key Words: anterior segment dysgenesis, eyelid coloboma, Panthera uncia, Peters' anomaly, Peters' plus syndrome, snow leopard

INTRODUCTION

Anterior segment dysgenesis (ASD) is induced by abnormalities during embryogenesis and cell differentiation. ASD has also been known as anterior chamber cleavage syndrome or keratolenticular dysgenesis.[1] The anomalies found in human ASD have been divided into three groups: central, peripheral, and combinations of both. The central malformations are characterized by posterior corneal defect, iridocorneal and keratolenticular adhesions. The peripheral malformations are characterized by a prominent Schwalbe's line, iris strands to Schwalbe's line, and hypoplasia of the anterior iris stroma.[1,2] Disease severity is variable, and there may be coexisting ocular abnormalities such as sclerocornea, microphthalmos, aniridia, and colobomas.[3] Multiple systemic malformations may include congenital heart disease, external ear abnormalities, hearing loss, structural defects of the central nervous system, spinal defects, cleft lip/palate, and genitourinary malformations.[3,4]

Peters' anomaly is a rare human congenital malformation of the anterior segment of the eye and is a subtype of ASD. ASD represents a heterogeneous group of congenital anomalies of the anterior segment of the eye and is often associated with other ocular and systemic abnormalities.

It affects the central cornea with adhesions between the iris and/or lens to the posterior corneal stroma, absence of Descemet's membrane and the corneal endothelium.[5] The condition is bilateral in 80% of human cases, carries a high risk of early onset glaucoma, found in 50% of the cases, and is often associated with poor vision. The etiology is diverse and includes developmental, environmental, and genetic causes.[6] However, the majority of the cases have no identifiable cause.[7] A small number of cases have been described in association with mutations of genes that play a role in the development of the eye.[6,8,9] Peters' anomaly is believed to arise as a result of abnormal keratolenticular separation, resulting in mechanical impairment of axial neural crest cell migration.[10,11] Neural crest derivatives comprise all of the tissues of the anterior segment including the corneal stroma, endothelium, and iris stroma.[12]

ASD is the most common cause of human congenital corneal opacities[13]; the prevalence is approximately

3/100 000 newborns.[14] Only a few cases in animals, including Springer spaniel [15] and Basenji dogs,[16,17] have been reported. In snow leopards, there have been reports of multiple ocular colobomas.[18,19] In 1985, there was a report on 16 snow leopards in Helsinki Zoo with different severity of multiple ocular colobomas, but no cause was determined.[20]

CASE REPORT

A male and a female snow leopard cubs were born in Rostock Zoo and were initially left undisturbed with their mother. At about 8 weeks of age, the animals were thoroughly examined. Both animals showed multiple ocular abnormalities with malformation of the anterior segment of the eyes and bilateral eyelid agenesis involving approximately 50% of the dorsal-temporal eyelids of both eyes (Fig. 1a–c). The size of both globes was normal in the male snow leopard, while the female had normal size right eye (OD) but a microphthalmic left eye (OS) (compared to the other eye, Table 1). Both animals did not follow a laser pointer beam, which may be a sign of impaired vision. The dazzle response and the pupillary light reflexes were positive in both animals. Ophthalmological examination by slit lamp biomicroscopy (KOWA SL-14; Torrance, CA, USA) was carried out. The left eye of the male cub had a superficial corneal ulcer three millimeter in diameter due to irritation from trichiasis because of the eyelid coloboma. Slit-lamp evaluation revealed shallow anterior chambers and a 360° circular area with strands from the iris collarette to the corneal endothelium in both eyes of both animals. A central white endothelial opacity 4–6 mm in diameter was visible in all four eyes (Fig. 1a–c). Examination after pharmacologic mydriasis revealed no synechia. Both lenses of the male and the right lens of the female exhibited minor opacities, while the microphthalmic left eye of the female had a mature cataract. It was not possible to examine the fundus of either animal. Intraocular pressure measured by applanation tonometry was 13 mmHg OD and 9 mmHg OS in the male, and 13 mmHg OD and 8 mmHg OS in the female. Ultrasound examination (B-5500, Technomed, Germany) was normal, except the left eye of the female that had a reduced axial length and a mature cataract. Both animals were humanely euthanized at an age of 53 days, and necropsies were performed. All eyes and eyelids were removed after euthanasia, and tissue samples from the kidneys, testicles, lungs, and the brain were fixed in 4% buffered formaldehyde and embedded in paraffin. Sections were cut at 4 μm and mounted on glass slides. The sections were stained with hematoxylin-eosin (HE).

Necropsy report

The male had internal hydrocephalus with a dilated ventricular system and an accumulation of cerebrospinal fluid (about 3 mL) in the ventricles of the brain. The female had no systemic pathologic findings.

Pathologic examination of the eyes of the male snow leopard Findings are listed in Table 1. The corneal epithelium was normally differentiated. The number of keratocytes in the posterior central corneal stroma was increased. A central defect in corneal stroma, endothelium, and Descemet's membrane was observed in both eyes. Endothelial cells were seen on the innermost surface. Iris strands to the termination of Descemet's membrane and to the periphery of the corneal defect were observed (Fig. 2a–e). The trabecular meshwork was normally developed. Both the iris and the ciliary body were hypoplastic. The right lens exhibited a subcapsular cataract.

Pathologic examination of the eyes of the female snow leopard The OS was microphthalmic (Table 1). The right globe exhibited malformations similar to those found in the male eyes described previously (Table 1). In the

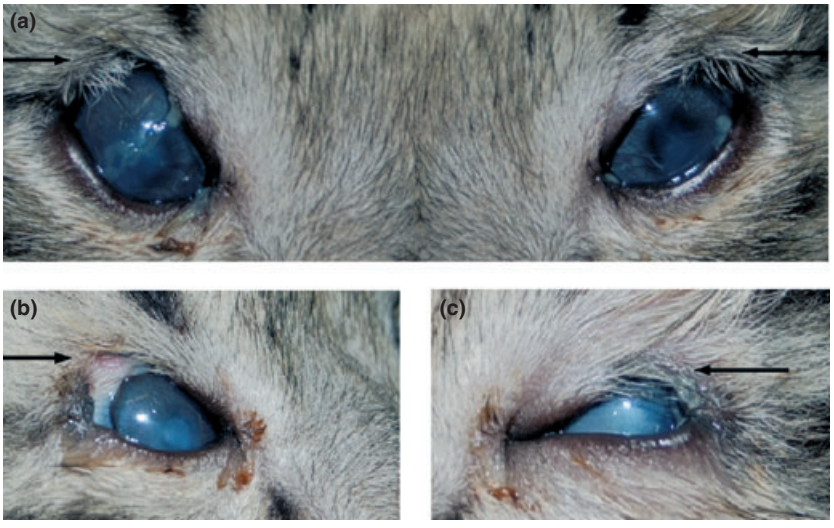

Figure 1. (a) The male snow leopard with bilateral upper eyelid colobomas (arrows) and central corneal opacities. The right eye (b) and the left eye (c) of the female snow leopard. The upper eyelids have colobomas (arrows). The corneas are opaque; the opacity on the left eye is more dense and the cornea slightly smaller in diameter.

Table 1. Findings in the eyes of the two snow leopards

	Male (both eyes)	Female OD	Female OS
Globe size	20 × 20 × 20 mm	19 × 20 × 20 mm	15 × 15 × 14 mm
Eyelids	Coloboma	Coloboma	Coloboma
Cornea	Central posterior corneal defect	Central posterior corneal defect	Central posterior corneal defect with stromal thinning
Anterior chamber	Iris strands	Iris strands	Iris strands
Iris and ciliary body	Hypoplastic	Hypoplastic	Hypoplastic. Iris adhered to cornea
Iridocorneal angle	Open	Open	Closed
Lens	Subcapsular cataract	Subcapsular cataract	Dense cataract
Choroid	Hypoplastic	Hypoplastic	Hypoplastic
Retina	Normal	Normal	Normal
Optic nerve	Normal	Normal	Normal
Vitreous	Normal	Normal	Remnant of hyaloid artery

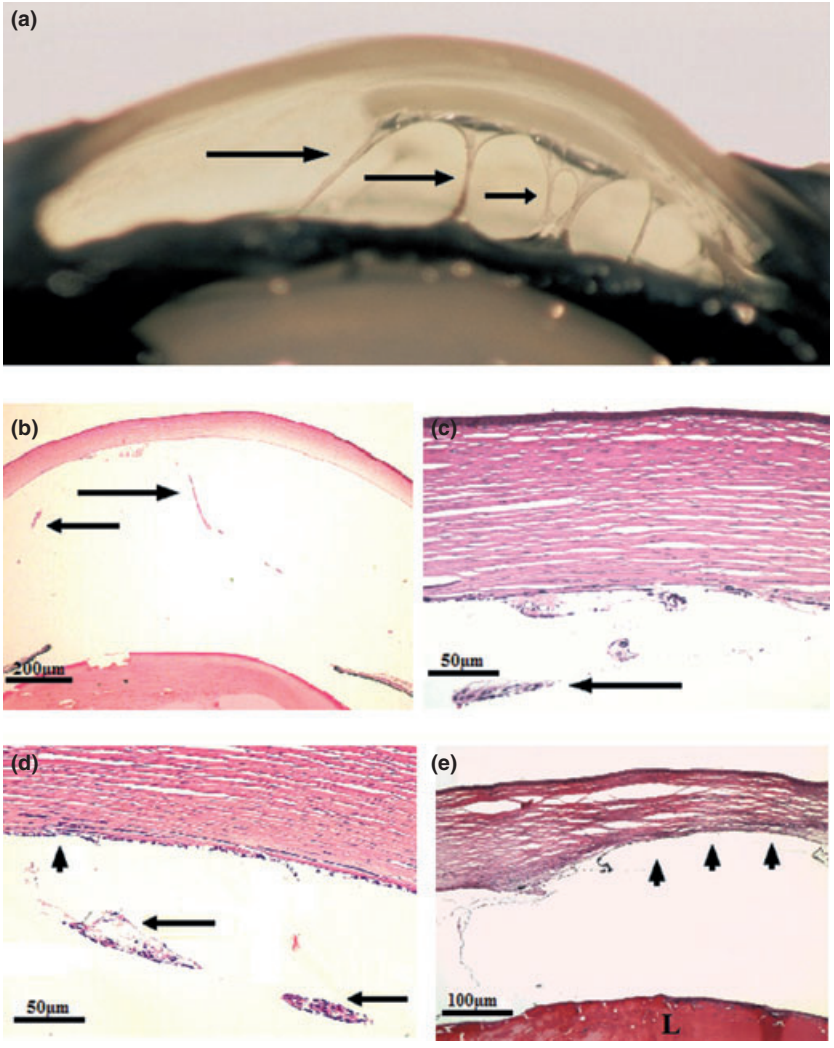

Figure 2. (a) Macroscopic view of the strands (arrows) from the corneal defect to the iris of the male snow leopard's left eye. (b) Histology shows the strands (arrows) between the cornea and the iris. (c) The cornea is seen without Descemet's membrane, and fibrovascular strands are noted on the posterior surface of the cornea and in the anterior chamber (arrow). In other areas (d), defects and ruptures in Descemet's membrane (arrowhead) are observed along with fibrovascular strands (arrows) in the anterior chamber. (e) In the left eye of the female snow leopard, a large posterior corneal defect (arrowheads) is shown. Iris is very hypoplastic and adhered to the posterior part of the cornea. Descemet's membrane is missing, and strands are seen from the cornea to the iris. The lens (L) is cataractous (b–e = HE staining).

female OS, the corneal epithelium was normal. There was a central stromal thinning with central posterior corneal defect (Fig. 2e). The iris was adhered to the posterior side of the cornea on one side. On the other side, the iris was hypoplastic. The iridocorneal angle was closed on both sides. There were iris strands between the posterior corneal defect and the iris. The ciliary body was hypoplastic, with cysts of the pigmented ciliary epithelium. The lens

demonstrated a dense cataract (Fig. 2e). The sclera was thickened, and the choroid was hypoplastic. In the vitreous body, there was a remnant of the hyaloid artery.

Histopathology of the kidneys, testicles, lungs, and the brain was without lesions in both animals. In particular, there was no indication of an inflammatory infiltration of the brain.

The gross and histological findings of both eyes of these two Snow Leopard cubs are identical to those of humans with Peters' anomaly. In addition to Peters' anomaly, there were colobomas of the upper eyelids, and the male also had hydrocephalus; thus, the male had some of the features of Peters' plus syndrome. The OS of the female snow leopard was microphthalmic with numerous malformations including absent trabecular meshwork, cataract, and a remnant of the hyaloid artery.

DISCUSSION

ASD refers to a spectrum of congenital abnormalities of the ocular anterior segment. The arbitrary classification of ASD in categories represents in reality a spectrum of disorders. ASD can be central, peripheral, or both. The peripheral anomalies range from posterior embryotoxon (a prominent anteriorly displaced Schwalbe's line) to Axenfeld's anomaly (iris processes attached to a prominent Schwalbe's line) to Rieger's anomaly (Axenfeld's anomaly with iris hypoplasia) and to its most severe form, Peters' anomaly, in which there can be both central and peripheral anomalies. Axenfeld and Rieger are both peripheral anomalies, and because of the similarities some have suggested the term Axenfeld-Rieger (AR),[21] and divided it into AR anomaly (without systemic signs) and AR syndrome (with systemic signs).[22] The central abnormalities in ASD represent a continuum from only posterior keratoconus (posterior corneal depression) to the more severe Peters' anomaly (corneal leukoma with adherent iris and/or lens). The corneal opacity is usually central, oval and sharply defined, with variable size and density. Recently, Peters' anomaly has been subdivided in type 1 (central corneal opacity with iridocorneal adhesions), type 2 (central corneal opacity with cataract or keratolenticular adhesions), and Peters' plus syndrome (Peters' anomaly in association with systemic malformations).[13]

ASD was previously referred to as 'mesodermal dysgenesis' because it was believed that the affected tissues are of mesodermal origin. This is now known to be incorrect. The tissues are primarily of neural crest origin.[23] The term 'anterior chamber cleavage syndrome' is no longer used as cleavage does not occur during anterior segment development.[23,24]

During week four after gestation, neural crest cells migrate from the developing neural tube and give rise to many of the structures of the eye.[25] The neural crest cells form the corneal endothelium, keratocytes, iris stroma cells, melanocytes, and trabecular meshwork. Later, the neural crest cells form a continuous layer extending from the cornea to the trabecular meshwork and onto the anterior surface of the iris becoming continuous with the pupillary membrane and tunica vasculosa lentis. Separation of the lens vesicle and the basement membrane of the surface ectoderm occurs.[23,26] If any failure of these developmental stages occurs, the anterior chamber will not develop properly, resulting in ASD. Keratolenticular dysgenesis is the primary event in the embryogenesis of Peters' anomaly, and the malformation in neural crest derivatives (including cartilage, bone, and connective tissue) occurs as a passive result of interference with their axial migration.[10,11,27] Dysgenesis of the aqueous drainage channels may be associated with developmental glaucoma. Failure of proper lens vesicle separation may result in a persistent keratolenticular adhesion.[23,26]

Snow leopards have been kept in Rostock Zoo since 1963. The first couple came from Sweden.

There are about 300 snow leopards kept in European Zoos according to information from the European Endangered Program (the breeding conservation program). Our current couple of breeding animals originated from Basel Zoo in Switzerland (female) and Neuwied Zoo in Germany (male) and arrived in Rostock in 2001 and 2006. The first noticed eye problem in Rostock Zoo occurred in 2007, when this couple mated the first time. The couple had one single pup with microphthalmia of the left eye and a clinically normal right eye. This pup had been destroyed but unfortunately no necropsy was performed. The same couple had eight puppies since 2007, but only one of these has been raised by the mother due to various causes. Two littermates had feline herpes virus infections (real time-PCR; Idexx VetMed Labor, Ludwigsburg, Germany); one died due to systemic disease, and the other recovered. All offspring before 2011 had no noticeable developmental or acquired eye disease, but died of various other reasons (anemia, parasites, myocarditis, myofibrosis). As a result of the ocular findings described in this paper, the Basel Zoo and Neuwied Zoo had been questioned about eye problems in their collections. Neither of them noticed any malformation in young snow leopard cubs. A genetic etiology is possible in this small gene pool.

We support that the well-established ASD terminology in humans is also applicable in animals. The present cases demonstrate the importance of a thorough ophthalmic and systemic examination of family members in animals having ocular malformations.

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