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Authors
Neilan, Edward
Pikman, Yana
Kimonis, Virginia E

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CASE REPORT

Peters Anomaly in Association with Multiple Midline Anomalies and a Familial Chromosome 4 Inversion

Edward Neilan, Yana Pikman, and Virginia E. Kimonis
Division of Genetics, Children's Hospital, Harvard Medical School, Boston, MA, USA

We describe the clinical presentation of a boy with Peters anomaly and a cataract of the left eye in association with multiple midline defects. His extraocular developmental abnormalities include cleft lip and palate, cardiac anomalies, an atretic cranial meningocele, as well as malformation of the left ear with chronic otitis media. Genetic analysis revealed a balanced paracentric inversion of chromosome 4, inv(4)(q12q13.3), also present in his asymptomatic father and siblings. His normal stature and cognitive development distinguish this case from the Peters Plus syndrome. The presence of a cranial meningocele represents a new association with Peters anomaly.

Keywords Peters anomaly; meningocele

INTRODUCTION

Peters anomaly is a defect in the development of the anterior chamber of the eye. There is a range of features that can be part of this phenotype. They include central corneal opacity (leukoma), thinning of the posterior aspect of the cornea, and iridocorneal adhesions attached to the edges of the leukoma.[1,2] Sclerocornea, posterior keratoconus, and posterior embryotoxon are also frequently associated. The corneal endothelium is derived from the neural crest cells and these anomalies are thought to be due to a defect in neural crest cell migration.[3] The condition has been reported in association with intrauterine infection, maternal alcohol ingestion, chromosome abnormalities, and several single gene defects.[4]

Peters anomaly was originally thought to occur as an isolated malformation, but was later found to be often associated with systemic defects.[2,3,5,6] Peters Plus syndrome has been used to describe the association of Peters anomaly with short stature, small hands, mental retardation, abnormal ears, and cleft lip and palate.[1,6,7]

CASE REPORT

Our patient was born at term to a G3P2 Chinese mother via normal spontaneous vaginal delivery, weighing 7 pounds and 15 ounces, and measuring 20 inches in length. The pregnancy was uncomplicated, with no smoking, alcohol, or other teratogenic exposures. The mother received good prenatal care and had three fetal ultrasounds, which were reported as normal.

At birth, the boy was found to have several anomalies, including left microphthalmia with anterior dysgenesis, dysplastic retina, and cataract, consistent with a Peters anomaly. There was no response to visual stimulation on the left side even with the brightest light. His right eye was normal. He also had a left unilateral incomplete cleft lip, cleft alveolus, and complete cleft of the left secondary palate. The left ear was slightly smaller and abnormally cupped compared to the right side (Fig. 1).

He was noted to have a soft nodule on the posterior midline parietal scalp surrounded by a ring of long, dark, coarse hair and lying within an area of capillary hemangiomata. A separate congenital pigmented nevus was present to the right of the midline scalp (Fig. 2). Neuroimaging revealed a defect in the parietal bone and continuity of the nodule with the dura consistent with an atretic parietal meningocele and associated with a persistent falcine sinus (Fig. 3). The meningocele was surgically removed at nine months of age. Immunohistochemistry demonstrated positive staining for epithelial membrane antigen (EMA), a meningeal antigen, and was negative for glial fibrillary acidic protein (GFAP), a glial cell antigen.

Echocardiography showed the patient's cardiac abnormalities to include an anterior malalignment ventricular septal defect, atrial septal defect, right aortic arch with an aberrant left subclavian artery, and a patent ductus arteriosis, creating the anatomic potential for a vascular ring. The patent ductus arteriosus and septal defects were repaired at two months of age.

Genetic analysis showed a paracentric inversion of chromosome 4, inv(4)(q12q13.3). Genetic evaluation of the patient's

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Address correspondence to Virginia E. Kimonis, M.D., MRCP, Children's Hospital, Division of Genetics & Metabolism, 300 Longwood Avenue, Fegan 10, Boston, MA 02115, USA. E-mail: virginia.kimonis@childrens.harvard.edu

FIG. 1. Frontal view of patient at age 3 months. Note left microphthalmia, cleft lip, and small cupped left ear.

parents as well as two older siblings showed the phenotypically normal father and both siblings to possess the same chromosome inversion.

As the child developed, he suffered from chronic otitis media with Eustachian tube dysfunction and conductive hearing loss. He was found to have a narrowing of the left external auditory canal and underwent a myringotomy with insertion of tubes, which improved his hearing. An auditory brainstem response (ABR) showed normal hearing in both ears after tube placement.

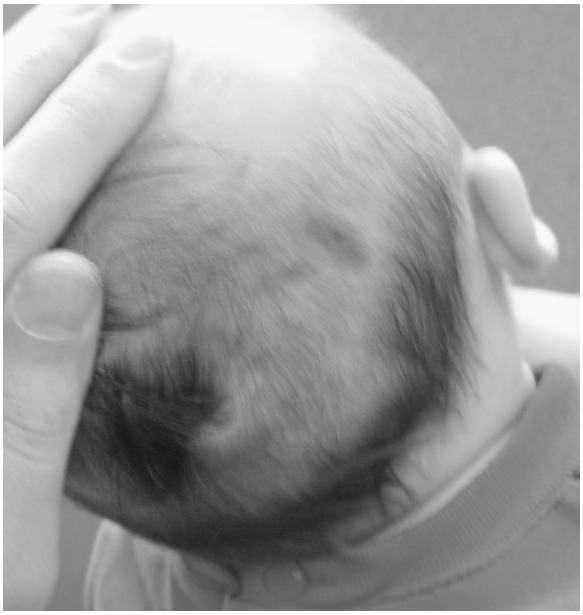

FIG. 2. View of scalp of patient at age 3 months demonstrating the hair collar sign: a tuft of longer hair and a capillary hemangioma surrounds the atretic meningocele. Note also the laterally located pigmented nevus.

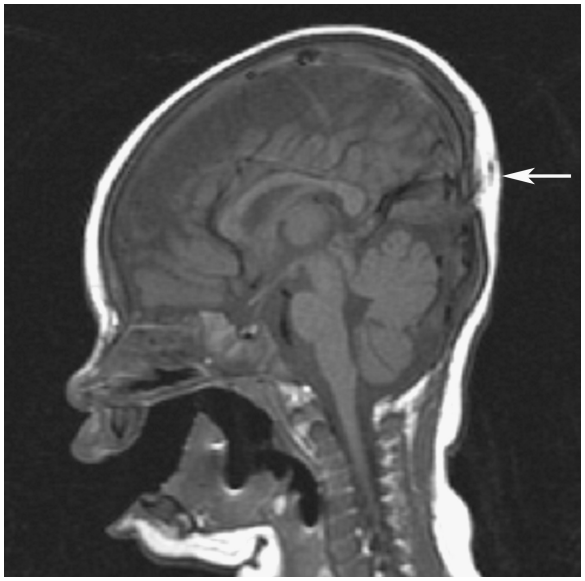

FIG. 3. T1-weighted brain MRI of the patient at age 6 months. The arrow indicates the location of the atretic parietal meningocele overlying a persistent falcine sinus. There were no other structural abnormalities of brain.

The child's development to date has been normal. His height and weight have remained in the 50th percentile throughout his first two years of life. Head circumference always stayed above the 25th percentile. He has some speech delay, which may be associated with his numerous treatments and hearing problems, and he currently receives speech therapy.

DISCUSSION

Peters anomaly has been associated with a constellation of malformations including short stature, mental retardation, CNS abnormalities, and cardiac and urogenital defects to make up the Peters Plus syndrome. The etiology of this disease is thought to be a defect in neural crest cell migration thus accounting for the constellation of symptoms. Here, we report the association of Peters anomaly with several CNS as well as midline defects. In Peters Plus syndrome, CNS defects have been reported to include microcephaly, mild to moderate mental retardation, and arrested hydrocephalus.[3,4,6] Urogenital abnormalities, including cryptorchidism and hypospadias have also been reported.[4,6] Cardiac defects are also part of the constellation of midline-associated defects. Cardiac defects, especially atrial septal defects and ventricular septal defects, are associated with a significant number of reported Peters Plus syndrome cases.[3,6]

In our case report, the association of Peters anomaly with a cranial meningocele, the absence of mental retardation, and the presence of cardiac defects and a cleft lip and palate form a unique constellation of symptoms which does not fall within the Peters Plus syndrome.

The patient's hair around the nodule is consistent with a hair collar sign. This has been associated with neural tube closure defects of the scalp.[8] This pattern was recognized as early as 1938, first described in the association with a parietal scalp defect. In their evaluation of four patients with hair collar sign, Drolet et al.[8] found two patients to have encephaloceles, the third to have heterotopic brain tissue, and the fourth to have an atretic encephalocele. A definite bony defect and a small intracranial communication were identified in each case. In our patient, the hair collar sign along with the associated nodule pointed to the possibility of an underlying cranial defect, with MRI imaging and pathology confirming the presence of a meningocele.

There are several genetic defects reported to be associated with Peters anomaly. Mutations within the RIEG1 homeobox gene on chromosome 4q25 have been reported with the Rieger syndrome, and a 3′ splice-site mutation within the 3rd intron of that gene (IVS3-2A > T) is associated with unilateral Peters anomaly.[9] PAX6, on chromosome 11 at 11p13, has been associated with autosomal dominant Peters anomaly.[10,11] There have also been reports of Peters anomaly associated with mutations in PITX3, located at 10q25, and CYP1B1, located at 2p22.[12] The diverse array of genetic abnormalities associated with Peters anomaly makes this a polygenic defect.

In our report, the patient, his father, and two siblings possessed a paracentric inversion of chromosome 4, inv(4)(q12q13.3), with the family members being asymptomatic. It is possible that a disruption of a critical gene occurred at one of the breakpoints of this familial chromosome inversion and our patient also bears a mutation in the second allele of this same gene, thus revealing the locus of a new recessive disorder. Genes in this region of the chromosome include PDGFR-alpha, KIT, and EphA5. The ephrin receptor gene family, which includes (EphA5), has been implicated in the development of the central nervous system and may underlie the establishment, maintenance, and remodeling of patterns of cellular organization.[13]

The unique features of this case, including unilateral Peters anomaly in association with cleft lip and palate, heart defects, and meningocele, represent a pattern separate from the Peters Plus syndrome, as the patient does not have the defining characteristics of short stature and mental retardation. Considering that Peters anomaly has been associated with multiple genes and a wide range of features, physicians should evaluate each Peters anomaly case with great care and specific considerations for other associated midline anomalies and the possibility of normal height and development. Patients noted to have Peters anomaly should be screened for other malformations, especially those involving the midline structures, such as the pituitary gland and the heart.[2]

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