PRINT: ISSN 0972-3757 ONLINE: 2456-6360
Int J Hum Genet, 9(3-4): 255-261 (2009)
DOI: 10.31901/24566330.2009/09.03-4.07

A Case with the Combination of Bilateral Microphthalmia, Unilateral Pulmonary Agenesis, Diaphragmatic Eventration and Atrial Septal Defect: PDAC Syndrome

Metin Demirkaya[1], Betül Sevinir[1], Yakup Canitez[2], Özlem Bostan[3] and Meral Yildiz[4]

Department of Pediatric Oncology[1], Pediatric Allergy[2], Pediatric Cardiology[3], Ophthalmology[4], Faculty of Medicine, Uludag University, Bursa, Turkey

KEYWORDS Microphthalmia. Pulmonary Agenesis. Congenital Heart Disease

ABSTRACT The combination of pulmonary agenesis and anophtalmia or microphthalmia has been described previously. This condition is known as Matthew-Wood syndrome and PDAC syndrome (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect). We report a sporadic case of female infant with the combination of bilateral microphthalmia, unilateral right pulmonary agenesis and diaphragmatic eventration in addition to atrial septal defect (ASD) suggesting PDAC syndrome.

INTRODUCTION

Anophthalmia and microphthalmia are clearly defined malformations. On the other hand, primary unilateral pulmonary agenesis is also a known but a rare pathology (Toriello et al.1985; Campanella and Odell 1987; Sharma et al. 2005). Mostly, it appears sporadically. There have been several reports describing the association of pulmonary agenesis with anophtalmia or microphthalmia (Seller et al. 1996; Berkenstadt et al. 1999; Li and Wei 2006). A variety of other defects was described previously with these malformations (Priolo et al. 2004; Robert Lee et al. 2006). While this condition was previously described as Matthew-Wood syndrome, Chitayat et al. defined it as PDAC syndrome (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect) in 2007.

A case of a female infant with the features of PDAC syndrome including bilateral microphthalmia and unilateral right pulmonary agenesis, diaphragmatic eventration**,** in addition to ASD was reported.

CASE REPORT

The third child of a healthy non-consanguineous Caucasian couple aged 30 and 34 years has been referred to our University Hospital with eye malformations. The gestational age was 38 weeks and the birth weight was 3600 gr. She was delivered via caesarian section and had no remarkable problems except congenital eye malformations.

Regarding the family history, the first child was born prematurely (30 weeks) with gastroschisis and volvulus, who had been operated and died at the 20th day of birth. The second child is now a 9-year-old healthy boy.

On physical examination on 50th days, bilateral microphthalmia (more severe on the left side), right iris coloboma and depressed nasal bridge were detected (Fig. 1). On the left orbital border, there was a congenital cystic mass with the dimensions of 2x1 cm (Fig. 2). Chest radiography and the thoracic tomography imaging showed right pulmonary agenesis and diaphragmatic eventration (Fig. 3 and 4). Cranial magnetic resonance imaging (MRI) indicated bilateral microphthalmia. ASD and cardiac dextroposition were determined by echocardiography. Her chromosome analysis showed a normal 46 XX female karyotype. The child is now 36 months old growing in normal ranges without any other systemic disorders (Fig. 5). During follow-up, her psychomotor development was normal and social contact was even better than her peers. Written permission was taken from his parents for publication of this report and photography.

DISCUSSION

The combination of pulmonary agenesis and

Address for correspondence:
Dr. Metin Demirkaya, M.D.
Uludag Üniversitesi Tip Fakültesi, Çocuk Sagligi ve Hastaliklari AD, 16059 Görükle, Bursa, Turkey
Business Telephone: 00 90 224 2950432
Fax: 00 90 224 4428143
E-mail: demirkaya@uludag.edu.tr

anophthalmia or microphthalmia has been described previously. A variety of other defects were described previously with these malformations (Pierson et al. 2002). It appears similar to the case of Spear et al. (1987) with bilateral pulmonary agenesis, microphthalmia and VSD. Priolo et al. (2004) has reported a case of bilateral microphthalmia, bilateral pulmonary hypoplasia, unilateral diaphragmatic hernia and ASD. Here, a case of unilateral pulmonary agenesis with diaphragmatic eventration**,** bilateral microphthalmia and ASD was reported.

In addition to these findings, there was also a congenital cystic lesion on the left lower orbital border that was not enlightened via biopsy.

In the previous reports, mostly severe malformations including bilateral pulmonary agenesis were described which resulted with early death (Priolo et al. 2004; Li and Wei 2006; Robert Lee et al. 2006, Chitayat et al. 2007). In the present case, there was only unilateral (right) pulmonary agenesis explaining why no respiratory problems occurred so far.

In most previously reported cases of pulmo-nary agenesis, there were diaphragmatic defects (Berkenstadt et al. 1999; Priolo et al. 2004; Chitayat et al. 2007). The present case also had diaphra-gmatic eventration on the site of pulmonary agenesis.

During the 20th day of birth, there was a 5 mm wide ASD detected via echocardiographic examination, which showed the same condition in the next echocardiography which was perform-

Fig. 1. The patients photograph showing microphthalmia

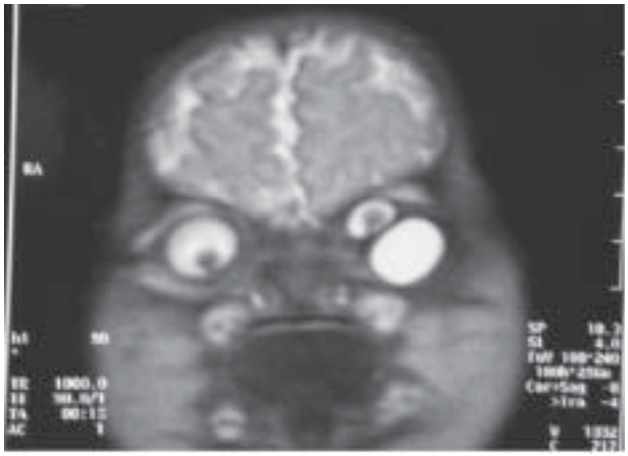

Fig. 2. Cranial MRI showing the cystic mass and microphthalmia

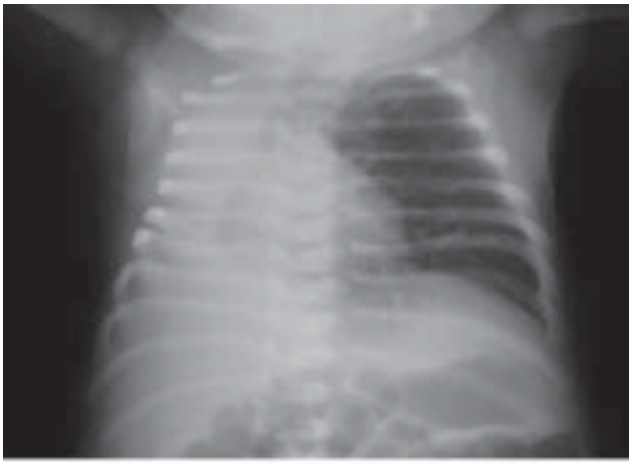

Fig. 3. Postero-anterior chest radiography showing right lung agenesis

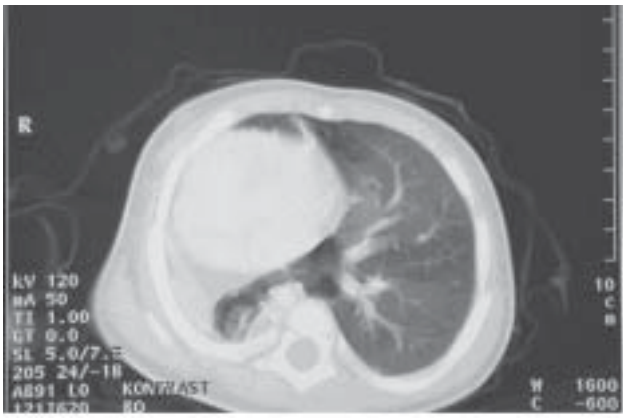

Fig. 4. Thorax computerized tomography showing right lung agenesis

Fig. 5. The photograph of the patient when she was 24 months old

Table 1. The clinical manifestastations in the previously reported cases and present case

Findings	*Present case*	*Spear et al. -1987*	*Seller et al. -1996*	
Number of cases	1	1	2	
Pulmonary malformation	Agenesis (unilateral)	Agenesis (bilateral)	Hypoplasia (bilateral)	Hypoplasia (bilateral)
Diaphragmatic defect	Eventration (unilateral)	Eventration (unilateral)	-	-
Microphthalmia/ anophthalmia	Microphthalmia (bilateral), coloboma (unilateral)	Microphthalmia (bilateral)	Anophthalmia (bilateral)	Anophthalmia (bilateral)
Cardiac malformation	ASD	VSD	-	Single ventricle, hypoplastic left atrium, enlarged pulmonary trunk
Facial dysmorphism	+	-	+	+
Urogenital abnormalities	-	-	-	Bicornuate, hypoplastic uterus
IUGR	-	-	-	+
Polyhydramnios	-	-	-	-
Karyotype	46,XX	46,XY	46,XY	46,XX
Sporadic/familial	Sporadic	Sporadic	Familial	Familial
Outcome	Alive	PND	PND	TOP, 18 weeks

Findings	*Berkenstadt et al. (1999)*	*Priolo et al. -2004*	*Li and Wei -2006*	*Robert Lee et al. (2006)*
Number of cases	1	1	1	1
Pulmonary malformation	Agenesis (unilateral)	Hypoplasia (bilateral)	Hypoplasia (bilateral)	Hypoplasia (bilateral)
Diaphragmatic defect	Hernia (unilateral)	Hernia (unilateral)	-	Hernia (unilateral)
Microphthalmia/ anophthalmia	Microphthalmia (bilateral)	Microphthalmia (bilateral)	Anophthalmia (bilateral)	Microphthalmia (bilateral)
Cardiac malformation	?	ASD	Dilated right atrium and vetricle, small left atrium and ventricle, two pulmonary ven	-
Facial dysmorphism	?	?	-	-
Urogenital abnormalities	?	Malrotated left kidney	Left hypoplastic pelvic kidney	-
IUGR	+	+	-	+
Polyhydramnios	+	+	-	-
Karyotype	46,XY	46,XY	46,XX	46,XX
Sporadic/familial	Sporadic	Sporadic	?	Sporadic
Outcome	TOP, 23 weeks	PND	PND	PND

Table 1: Contd....

Findings			*Chitayat et al. -2007*	
Number of cases			8	
Pulmonary malformation	Agenesis (unilateral), rudimentary (rigt lung)	Hypoplasia (bilateral)	Agenesis (bilateral)	Rudimentary (left lung), unilobar (right lung)
Diaphragmatic defect	Eventration (unilateral)	Hernias (bilateral)	Unilateral	Unilateral
Microphthalmia/ anophthalmia	Micro/anophthalmia (bilateral)	Microphthalmia (bilateral)	Microphthalmia (bilateral)	Bilateral
Cardiac malformation	VSD, hypoplastic left atrium	-	?	Hypoplastic right ventricle, pulmonary valve atresia, bicuspid aortic valve
Facial dysmorphism	+	+	+	+
Urogenital abnormalities	Bicournate and small uterus	-	?	Micropenis, bifid and hypoplastic scrotum
IUGR	-	-	-	+
Polyhydramnios	-	-	+	+
Karyotype	46,XX	46,XY	?	46,XY
Sporadic/familial	Familial	Familial	Familial	Sporadic
Outcome	PND	TOP	PND	TOP

Findings			*Chitayat et al. -2007*	
Number of cases				
Pulmonary malformation	Aplasia (bilateral)	-	Unilobar lungs (bilateral)	Unilobar lungs (bilateral)
Diaphragmatic defect	Bilateral	Unilateral	-	Unilateral
Microphthalmia/ anophthalmia	Microphthalmia (bilateral)	Microphthalmia (bilateral)	Micro/ anophthalmia (bilateral)	Micro/ anophthalmia (bilateral)
Cardiac malformation	Hypoplasia of both atrial appendages, VSD	-	ASD,PDA	Coarctation of the aorta, hypoplastic pulmonary arteries
Facial dysmorphism	+	+	+	+
Urogenital abnormalities	Hypoplastic uterus, vaginal atresia, right renal dysplasia	-	Hypoplastic left pelvic kidney, hypoplastic uterus	Hydronephrosis, atretic ureter
IUGR	+	-	-	-
Polyhydramnios	+	-	-	-
Karyotype	46,XX	46,XY	46,XX	46,XY
Sporadic/familial	Sporadic	Sporadic	Consanguineous parents	Sporadic
Outcome	PND	Alive	Post-operatively dead at 19 months	PND

IUGR, intrauterine growth retardation; ASD, atrial septal defect; VSD, ventricular septal defect; TOP, termination of pregnancy; PND, post-natal death, +,present; -,not present

ed at the 6th and 21st months. In the previous reports, several cardiac defects were described such as ASD, VSD, dilatation of right atrium in combination of pulmonary agenesis and congenital eye disorders (Spear et al. 1987; Seller et al. 1996; Priolo et al. 2004; Li and Wei 2006). Here, ASD and cardiac dextroposition was detected in association with right pulmonary agenesis, right diaphragmatic eventration and bilateral micropthalmia.

Chitayat et al. (2007) described PDAC syndrome, i.e. pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect. They showed evidences suggesting autosomal recessive inheritance. They thought that some previously described cases fit PDAC syndrome. In the present case**,** clinical findings such as bilateral microphthalmia, unilateral pulmonary agenesis, diaphragmatic eventration and cardiac defect (ASD) are the major findings of PDAC syndrome. Minor findings such as depressed nasal bridge was present; however, urogenital abnormalities were not. The clinical manifestations in the previously reported cases and present case are summarized in Table I.

In previous reports, the genetic basis of this pattern has not been clearly identified. In genetic etiology, there is probable autosomal recessive inheritance, abnormal chromozome-2p, mutations in STRA6 (Stra for "stimulated by retinoic asit") gene and loss of function of SOX2 gene. (Lurie et al. 1995; Seller et al. 1996; Say and Carpenter 1998; Ragge et al. 2004; Golzio et al. 2007; Pasutto et al. 2007). In some cases, it occurs sporadically (Priolo et al. 2004; Robert Lee et al. 2006). In the conventional cytogenetic analysis of this case, a 46 XX normal female karyotype was found.

STRA6 belongs to a novel group of retinoic acid (RA)-inducible genes that are likely to be direct targets of the retinoid receptors, such as RXRá and RARã (Bouillet et al. 1997). During embryogenesis, it is strongly expressed in the periocular mesenchyme, in the developing eyes, in respiratory mesenchymes, and in respiratory/bronchial epithelium, as well as in the developing CNS (meninges, cranial ganglia, choroid plexi, and brain microvasculature) and in different embryonic gut derivatives (the epithelium of the pharyngeal pouches, mesenchyme of the esophagus, stomach, intestine, and rectum) (Pasutto et al. 2007). Pasutto et al. (2007) showed that homozygous mutations in STRA6 cause a pleiotropic, multisystem malformation syndrome characterized by bilateral anophthalmia, mild facial dysmorphism, normal intrauterine growth, early lethality in most cases, and a variety of malformations of the lungs, diaphragm, heart, and urogenital system. Profound mental retardation and short stature with relatively large head were present in one of their patients with long-term survival having homozygous STRA6 mutation.

Golzio et al. (2007) undertook molecular analysis of STRA6 in two human fetuses from consanguineous families previously described as Matthew-Wood syndrome in a context of severe microphthalmia, pulmonary agenesis, bilateral diaphragmatic eventration, duodenal stenosis, pancreatic malformations, and intrauterine growth retardation. The fetuses had either a homozygous insertion/deletion in exon 2 or a homozygous insertion in exon 7 predicting a premature stop codon in STRA6 transcripts. In the same study, five other fetuses presenting at least one of the two major signs of clinical anophthalmia or pulmonary hypoplasia with at least one of the two associated signs of diaphragmatic closure defect or cardiopathy had no STRA6 mutations.

The present case has some findings consistent with STRA6 mutation, however her malformations were not as severe as STRA6 and in addition, her psychomotor development is excellent at the age of 3 years.

Regarding to family history, first child had isolated gastroschisis and died after 20 days of birth. There is known environmental and genetic effects on gastroschisis. (Torfs et al. 1994; Reece et al. 1997). The situations of the both siblings may be associated with the role of undetermined environmental and genetic reasons.

REFERENCES

Berkenstadt M, Lev D, Achiron R, Rosner M, Barkai G 1999. Pulmonary agenesis, microphthalmia, and diapragmatic defect (PMD): New syndrome or association? *Am J Med Genet*, 86: 6-8.

Bouillet P, Sapin V, Chazaud C, Messaddeq N, Decimo D et al. 1997. Developmental expression pattern of Stra6, a retinoic acid-responsive gene encoding a new type of membrane protein. *Mech Dev*, 63: 173-186.

Campanella C, Odell JA 1987. Unilateral pulmonary agenesis. A report of 4 cases. *S Afr Med J*, 71: 785-787.

Chitayat D, Sroka H, Keating S, Colby RS, Ryan G et al. 2007. The PDAC syndrome (pulmonary hypoplasia/agenesis, diaphragmatic hernia/eventration, anophthalmia/microphthalmia, and cardiac defect)

(Spear syndrome, Matthew-Wood syndrome): Report of eight cases including a living child and further evidence for autosomal recessive inheritance. *Am J Med Genet* Part A, 143A: 1268-1281.

Golzio C, Martinovic-Bouriel J, Thomas S, Mougou-Zrelli S, Grattagliano-Bessieres B et al 2007. Matthew-Wood syndrome is caused by truncating mutations in the retinol-binding protein receptor gene STRA6. *Am J Hum Genet*, 80: 1179-1187.

Li L, Wei J 2006. A newborn with anophthalmia and pulmonary hypoplasia (the Matthew-Wood syndrome). *Am J Med Genet A*, 140: 1564-1566.

Lurie IW, Ilyina HG, Gurevich DB, Rumyantseva NV, Naumchik IV et al 1995. Trisomy 2p: analysis of unusual phenotypic findings. *Am J Med Genet*, 55: 229-236.

Pasutto F, Sticht H, Hammersen G, Gillessen-Kaesbach G, FitzPatrick DR et al. 2007. Mutations in STRA6 cause a broad spectrum of malformations including anophthalmia, congenital heart defects, diaphragmatic hernia, alveolar capillary dysplasia, lung hypoplasia, and mental retardation. *Am J Hum Genet*, 80: 550-560.

Priolo M, Casile G, Lagana C 2004. Pulmonary agenesis/hypoplasia, microphthalmia and diaphragmatic defects: report of an additional case. *Clin Dysmorphol*, 13: 45-46.

Pierson DM, Subtil A, Taboada E, Butler MG 2002. Newborn with anophthalmia and features of Fryns syndrome. *Pediatr Dev Pathol*, 5: 592-596.

Ragge NK, Lorenz B, Schneider A, Bushby K, de Sanctis L et al 2005. SOX2 anophthalmia syndrome. *Am J Med Genet A*, 135: 1-7.

Reece A., Thornton J, Stringer MD 1997. Genetic factors in the aetiology of gastroschisis: a case report. *Eur J Obstet Gynecol Reprod Biol*, 73: 127-128.

Robert Lee SY, Shiu YK, Ng WF, Chow CB 2006. Another patient with pulmonary hypoplasia, microphthalmia and diaphragmatic hernia. *Clin Dysmorphol*, 15: 43-44.

Say B, Carpenter NJ 1998. Pulmonary agenesis: importance of detailed cytogenetic studies. *Am J Med Genet*, 76: 446.

Seller MJ, Davis TB, Fear CN, Flinter FA, Ellis I, Gibson AG 1996. Two sibs with anopthalmia and pulmonary hypoplasia (the Matthew-Wood syndrome). *Am J Med Genet*, 62: 227-229.

Sharma S, Kumar S, Yaduvanshi D, Chauhan D 2005. Isolated unilateral pulmonary agenesis. *Indian Pediatr*, 42: 170-172.

Spear GS, Yetur P, Beyerlein RA 1987. Bilateral pulmonary agenesis and microphthalmia. *Am J Med Genet Suppl*, 3: 379-382.

Torfs CP, Velie EM, Oechsli FW, Bateson TF, Curry CJ 1994. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology*, 50: 44-53.

Toriello HV, Higgins JV, Jones AS, Radecki LL 1985. Pulmonary and diaphragmatic agenesis: report of affected sibs. *Am J Med Genet*, 21: 87-92.