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An Additional Patient with Mycophenolate Mofetil Embryopathy: Cardiac and Facial Analyses

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We describe an infant male of Cambodian background who has typical craniofacial features of mycophenolate mofetil (MMF) embryopathy and a complex congenital heart defect (CHD) (double outlet right ventricle, mitral atresia, pulmonic stenosis, and total anomalous pulmonary venous return). Together with four case reports and the 20 patients included in two recent reviews, we report 24 (19 affected, five normal) patients with this pattern of anomalies. Eight (33%) have a CHD, most commonly, conotruncal or aortic arch defects (6/8, 75%). This would support the hypothesis that disturbance of cranial neural crest migration occurs in exposed infants, and may predict which additional anomalies will be observed in the future. We also attempted to score the severity of the facial anomalies in each MMF patient using a system created by plastic surgeons for patients with hemifacial microsomia. This classification had modest utility in comparing severity and correlating facial to extracranial defects. The findings are viewed with caution because of the preliminary methodology. Finally, since several exposed infants have been reported to be minimally affected, we remind clinicians to be sensitive to the potential mild expression of the effects of this teratogen. This awareness may influence clinical management of apparently normal MMF-exposed individuals.

Key words: cardiovascular malformation; congenital heart defect; conotruncal; microtia; mycophenolate mofetil; teratogen

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INTRODUCTION

The description of in utero exposure to mycophenolate mofetil (MMF, Cellcept®) has progressed from brief listings in transplantation registry proceedings [Armenti et al., 2004; Sifontis et al., 2006] to more detailed and illustrated case reports, which often include an updated review of the literature [Huang et al., 2008; Anderka et al., 2009; Dei Malatesta et al., 2009; Jackson et al., 2009; Parisi et al., 2009; Koshy et al., 2010]. Thoughtful commentaries [Carey, 2008; Vento et al., 2008; Anderka et al., 2009; Merlob et al., 2009] have discussed whether MMF should be considered a *bonafide* teratogen. Recently, a survey attempted to balance the flurry of case reports of affected fetuses and infants by trying to estimate the magnitude of the absolute risk of exposure to the mother and fetus [Klieger-Grossman et al., 2010].

This article describes another severely affected patient with what is generally acknowledged as the "MMF embryopathy," highlighting that the phenotype is sufficiently distinctive such that it was diagnosed from photographs prior to knowledge about the exposure history. We discuss the frequent occurrence of congenital heart defects (CHDs), especially conotruncal defects, which may provide insight into the role of neural crest cell migration and maldevelopment in this condition. We also study some of the facial features in MMF-exposed cases using a classification system developed for another malformation complex (hemifacial microsomia, HFM), but adapted for MMF exposure because of the observation of facial asymmetry, at least in our patient.

METHODS

We describe the clinical findings of a new patient and review the literature of individuals with in utero exposure to MMF. When

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possible, we focused on the type of CHD and facial defects. These were further evaluated using a nosologic system for classifying craniofacial anomalies in patients with HFM [O.M.E.N.S., Vento et al., 1991; expanded by Horgan et al., 1995]. The suggestion to use OMENS was proposed by the originator who had reviewed photos of our patient (John B. Mulliken, M.D., personal communication). In the OMENS system (as we will refer to it in our study), O refers to orbital distortion, M is for mandibular hypoplasia, E is for ear anomaly, N is for seventh cranial nerve involvement and S is for soft tissue deficiency. A brief summary of the individual component scores includes: O_0 normal—O_3 abnormal orbital size and position; M_0 normal mandible—M_3 complete absence; E_0 normal ear—E_3 severe microtia; N_0 no involvment—N_3 all branches involved, S_0 No involvement—S_3 severe soft tissue involvement. The OMENS system was drastically adapted for this study since neither personal examination nor imaging tests were available in many cases, and scoring relied on published text and photographs. The MMF-exposed patients were compared to determine if there was a correlation between those with the highest scores and the type of CHD, or other internal anomalies.

CLINICAL REPORT

This small for gestational age male was born at 40 weeks gestation to a non-consanguineous 22-year-old Cambodian G2P1 → 2 mother and 45-year-old Cambodian father. The mother of the propositus has Senior-Loken disease, with secondary anemia, and is legally blind. She received a kidney transplant at the age of 16 years; her affected younger brother also has visual impairment, kidney stones and underwent a kidney transplant at age 12 years. Her first pregnancy resulted in the birth of a healthy girl, who is now 4 years old. It was reported through social services that she had been on no medications during that pregnancy because they "made her ill." It is not known whether she took medications early on and stopped them when she became ill, or if she did not take any medications from the time of conception. During the first trimester of this current pregnancy, she received MMF immune-suppression at a dose of 1 g/day. Additionally, there was a massive ingestion (reportedly, the entire contents of a bottle) at approximately 2-month gestation in an acknowledged suicide gesture following a domestic dispute. Attempts to obtain details about the quantity and timing of this ingestion were declined. MMF was discontinued at 3 months gestation when the pregnancy was diagnosed. Other medications used prior to conception and continued throughout pregnancy included prednisone 5 mg daily, tacrolimus 6 mg daily, omeprazole 20 mg daily, and ferrous sulphate 600 mg daily.

Fetal movements were reported as normal. Prenatal ultrasonography showed CHDs (double-outlet right ventricle with large anterior aorta, small posterior artery, and pulmonic stenosis), a two-vessel cord, and intrauterine growth retardation with a 2-week growth lag. Maternal serum screening reported a 1:10,000 risk for trisomy 18 (no other analyte values available) and amniocentesis was declined. Maternal laboratory testing included blood type O^+, and negative titers for RPR, rubella, hepatitis B surface antigen, and human immunodeficiency virus. The baby was delivered by cesarean because of a non-reassuring fetal cardiac pattern. Apgar scores were 4 and 9 at 1 and 5 min, respectively.

At birth the weight was 2,064 g, length was 46 cm, and head circumference was 32 cm (<3rd, 10–25th, 10th centiles, respectively). The baby had severe bilateral microtia (length 2 cm) with an absent external auditory meatus (Fig. 1). The fontanelle was enlarged (4.5 × 3.5 cm). There was bilateral microphthalmia (inner canthal distance 2.0 cm, 50th centile), severe on the left (not measured) and mild on the right (palpebral fissure 1.5 cm, <5th centile) with an inferior iris coloboma. Formal ophthalmology examination showed that the baby had severely limited vision in both eyes with probably no more than light perception. Early intervention by the Braille Institute was recommended. Additional craniofacial anomalies included mild asymmetry with slight hypoplasia of the lower face, micrognathia, moderate ankylosis of the jaw, a large cleft of the hard and soft palate, and two skin tags on the left side between the ear and mouth (one flat, another with a central depression). The hearing screen was not completed. On the initial radiographs, the clavicles were described as hypoplastic and angulated, the ribs as thin, and the scapulae as hypoplastic; subsequent radiographs only referred to hypoplastic scapulae. Additional features included a short neck with webbing, narrow shoulders, mild rhizomelic shortening, and bilateral cryptorchidism.

The echocardiogram performed on the second day of life showed a double outlet right ventricle, normally related great arteries, large membranous to outlet ventricular septal defect, moderate secundum atrial septal defect, mild to moderate right peripheral pulmonic stenosis, severe valvular and infundibular pulmonary stenosis, moderately hypoplastic pulmonic valve, interrupted inferior vena cava, and total anomalous pulmonary venous connection to the coronary sinus. The baby did not require prostaglandin infusion and a right modified Blalock-Taussig shunt was created on the 10th postnatal day. MRI study of the brain and ultrasonographic examination of the kidneys were within normal limits. MRI evaluation of the inner ear structures has been postponed until cardiac surgery is complete.

Genetic testing for Treacher Collins syndrome (*TCOF1* mutation analysis) and CHARGE syndrome (*CHD7* sequencing and duplication/deletion analysis) were both normal. The chromosome and chromosome microarray analyses (Signature Chip OS, Version 1.1; Agilent 105K Oligo, Spokane, WA) were also normal. At this point, bilateral HFM (also known as craniofacial microsomia) was considered the most appropriate diagnosis. MMF embryopathy was suggested by an independent geneticist (A.E.L.) who reviewed the patient's photographs without knowledge about the maternal exposure.

The baby had severe respiratory distress and failure to thrive, for which he required tracheostomy and a gastrostomy tube. At follow-up at age 9 months, his facial appearance was unchanged. Hospitalized since birth with the tracheostomy, he has global developmental delays, but is viewed as making progress. He has hypotonia with decreased head and trunk control, is unable to sit, roll, or hold a bottle, but can play with his toes. He has very limited vision and has light perception. He has been transferred to a skilled chronic care nursing facility while he gains enough weight to undergo additional cardiac surgery. Photographs at age 1 year show the left-sided facial tags and microphthalmia, more severe on the left (Fig. 2). A follow-up examination at age

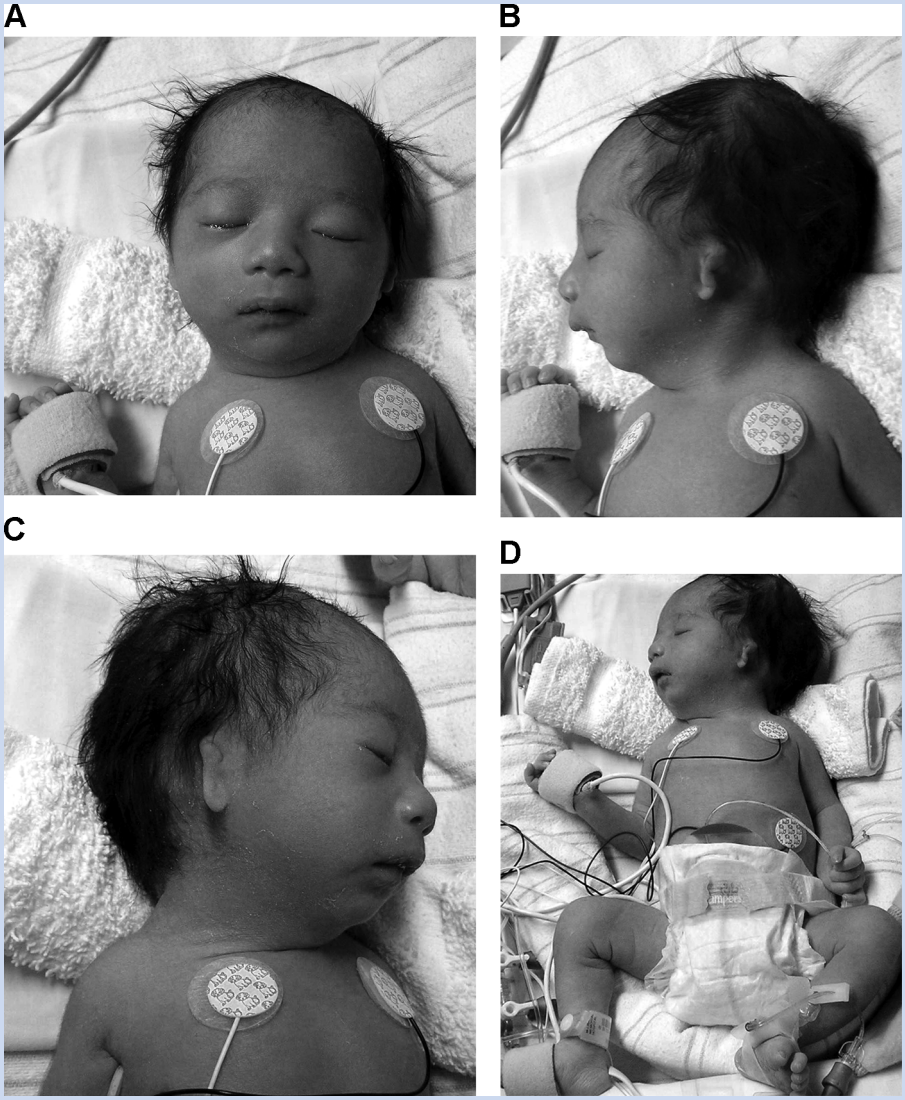

FIG. 1. Propositus at birth. A: Frontal facial appearance. Note subjective increased inner canthal distance, and subtle asymmetry of left mandible with mild soft tissue involvement. B,C: Compare micrognathia and microtia of both sides of the face. Ear tags are barely perceptible on the left cheek and pre-auricular region. D: Full body view shows the relatively narrow shoulders.

15 months was attempted, but the patient and family could not be located.

LITERATURE REVIEW

Adding this new patient to the series of 14 patients reported by Anderka et al. [2009], and single patients from Jackson et al. [2009], and Parisi et al. [2009]—all published in the same issue of this journal—plus, those of Huang et al. [2008], Dei Malatesta et al. [2009], and Koshy et al. [2010] increased the total number of affected patients to 19. In addition, we included five livebirths with "normal development" and no malformations from the 10 pregnancies (nine women) identified prospectively by Klieger-Grossman et al. [2010] using the Organization of Teratology Information Specialists (OTIS) network. We did not include the four miscarriages (two born to the same woman) and one elective termination in which clinical findings were not available. To avoid duplicative reporting, we point out that the infant girl described in detail by Parisi et al. [2009] was also cited by Anderka et al. 2009 [Table I, patient 7] and first mentioned as part of the National Transplantation Pregnancy Registry report [Sifontis et al., 2006, case 3]. The clinical findings of the total of 24 patients are presented in Table I.

RESULTS

Of the 24 total patients, half (12, 50%) had a similar phenotype with severe microtia and at least moderate micrognathia. Two had only hypoplastic fingernails and mild aortic arch defect [Pérgola et al., 2001] and one had a colobomatous orbital cyst with mild

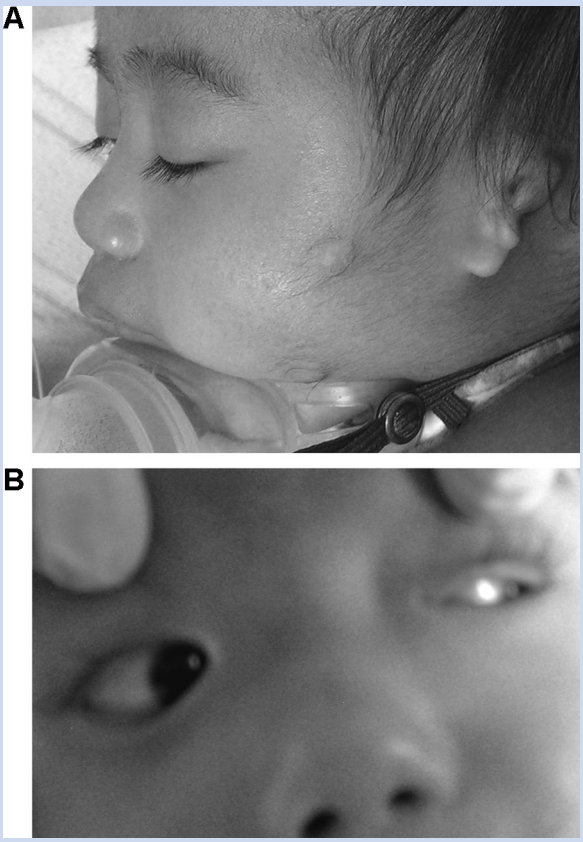

FIG. 2. At age 1 year. A: The left-sided pre-auricular skin tags are better viewed. B: There is bilateral microphthalmia, more severe on the left side.

microphthalmia [Dei Malatesta et al., 2009; personal communication from the author: child is developmentally well, without hearing loss or microtia]. Eight (33%) of the reported patients with MMF exposure had a CHD, six (75%) of which were either a conotruncal or aortic arch defect. In two cases, we interpreted the wording of the report so that, "aberrant blood vessel between trachea and esophagus" was viewed as a possible pulmonary artery sling [Pérgola et al., 2001], and the ventricular septal defect with an anterior aorta was suspected to be an outlet defect [El Sebaaly et al., 2007]. We compared the timing of the MMF ingestion with the presence or absence of a CHD, and whether the defects could be classified as conotruncal or not, but the small cohort size and incomplete exposure information precluded meaningful analysis (data not shown).

As listed on Table I, the three patients with the highest OMENS scores (9) were severely affected [# 15, Huang et al., 2008; # 9, Schoner et al., 2008; # 7, Jackson et al., 2009]. The four patients with the lowest scores (1–2) [# 4 Armenti et al., 2004; # 7 Sifontis et al., 2006; # 14 Andrade Vila et al., 2008; # 18 Dei Malatesta et al., 2009] had a mild clinical phenotype overall, as did patient no. 3 [Pérgola et al., 2001] with hypoplastic fingernails who could not be scored because of the lack of craniofacial information. Review of published photos did not detect evidence of HFM in other patients.

DISCUSSION

This new patient contributes to the understanding of MMF embryopathy in several ways. Although we cannot calculate a formal dose–response in all reported patients, the timing-outcome in the new patient can be assessed since the exposure to MMF was confined to the period before 12 weeks. In addition to the mother's maintenance dose, the fetus was exposed to an additional "massive" amount of MMF at approximately 2 months. Some aspects of the overall phenotype of this child are not as severe as in other patients who had lethal craniofacial and visceral anomalies [Schoner et al., 2008; Parisi et al., 2009]. This raises the possibility that there may be a lack of a dose–response relationship. The weakness in our case description is the lack of a precise pill count/dosing, and our difficulty to obtain detailed information from the mother.

The increase in the number of patients and the inclusion of apparently normal children [Klieger-Grossman et al., 2010] exposed to MMF helps to define the CHD and facial features. Aside from descriptive reports and comparison of images (for example, photographs, MRI scans), the assessment of phenotype severity is highly subjective. Our attempt to use the OMENS scoring system was not significantly helpful in this small series. For example, only the new patient had a possible mild soft tissue deficiency (S_{1L}). The difference between mild soft tissue deficiency and mandibular hypoplasia can be difficult to appreciate in any newborn with facial asymmetry. With aging, facial definition becomes more apparent, and with follow-up and scrutiny, such information may be more reliably assessed. It was difficult to score many literature cases, for example, fetal losses. One reason for using the OMENS system was to determine its utility on a well-studied patient, which might be impetus for additional studies. Future research could evaluate whether there are additional patients with asymmetry consistent with HFM, to follow over time, and irrespective of HFM, determine whether there is a correlation between the severity of the facial anomalies and extra-craniofacial defects.

Despite the small cohort, it is striking that two patients [our patient and Jackson et al., 2009] have double outlet right ventricle, which is an anatomically heterogeneous rare CHD [Obler et al., 2008]. Both patients also had mitral valve obstruction and pulmonic stenosis. In our patient, the great arteries were normally related, whereas the description of the other patient implied a malposed ("anterior") aorta. Double outlet right ventricle is often classified with other conotruncal CHDs such as truncus arteriosus. More recent understanding about the many genes and numerous subtypes implies pathogenetic diversity which may also include a looping defect [Obler et al., 2008].

Conotruncal and aortic arch CHDs occur in several malformation syndromes, including teratogenic exposures [Tables 2 and 3 in Lin et al., 2006]. The co-occurrence of this pattern of CHDs and microtia/anotia overlaps superficially with the retinoic embryopathy, although the retinoic acid embryopathy pinnae [Lammer, 1991] are not identical. Whereas the pattern of malformed external ears in fetuses exposed to isoretinoin includes an elongated tragus, vertically oriented and hypoplastic crus helicis and slit-like stenotic canal [Lammer, 1991], the small ears of MMF embryopathy resemble most images of typical "microtia, second degree," or "microtia, third degree" [Hunter et al., 2009], as in this new patient. Severe

TABLE I. MMF-Exposed Pregnancies in Which the Outcome Reported Clinical Findings (24 Total, Including New Patient)

					Modified OMENS score[a]						
Patients	Author year	MMF exposure	Other drugs	CHD	Orbital size	Mandible size	Ear size, shape	Facial nerve weakness, soft tissue deficiency	Total OMENS score	Skeletal defects	Other
1	Present case	1 g/day until 3 months, entire contents of bottle in one dose at approximately 2 months	Prednisone, 5 mg/day; tacrolimus, 6 mg/day; omeprazole, 20 mg/day; ferrous sulphate, 600 mg/day	DORV, NRGA; VSD, PS, mitral stenosis; TAPVR, IVC interruption	O_1	M_{1L}	E_3	N_0 S_{1L}	5	Hypoplastic scapulae	—
2	Anderka et al. [2009] [Pt 1]	2 g/day for 1 month; discontinued for 2 months; resumed the day before LMP, discontinued at 12 weeks	Prednisone, dose NS	—	O_0	M_1	E_3	N_0 S_0	4	—	—
3	Pérgola et al. [2001] [Pt 1 of Armenti et al., 2004; Pt 2 of Anderka et al. 2009]	Transplanted at 6–7 weeks; 2 g/day until 26 weeks; 1 g/day until delivery	Tacrolimus, 7 mg/day; prednisone, 25 mg/day	"Aberrant blood vessel between trachea and esophagus" (possible ARSCA)	Unk	Unk	Unk	Unk	Unk	Hypoplastic fifth fingers	Unk
4	Armenti et al. [2004], patient 7; [Pt 3 of Anderka et al., 2009]	1 g/day until 24 weeks	Tacrolimus, dose NS; prednisone, dose NS; sirolimus, began at 24 weeks, dose NS; ATG started at 24 weeks, dose NS	—	Unk	Unk	Yes, details Unk	—	Min 1	—	CL/P
5	Le Ray et al., 2004 [Pt 4 of Anderka et al., 2009]	500 mg/day until 13 weeks	Tacrolimus, 9 mg/day; prednisone, 15 mg/day; azathioprine, 50 mg/day, started at 13 weeks	—	Unk	M_2	E_3	N_0 S_0	5	—	TOP CL/P ACC, left pelvic kidney
6	Källén et al. [2005] [Pt 5 of Anderka et al., 2009]	"Early pregnancy," dose NS	Tacrolimus, dose NS; prednisone, dose NS	Complex cardiac defect, NS	Unk	Unk	Unk	Unk	Unk	—	Iris anomaly, esophageal atresia
7	Sifonis et al. [2006], Pt 4 [Pt 7 of Anderka et al., 2009]	2 g/day until 15 weeks	Tacrolimus, dose NS; prednisone, dose NS	—	Unk	Unk	Yes, details Unk	Unk	Min 1	—	—
8	Tjeertes et al. [2007] [Pt 8 of Anderka et al., 2009]	Throughout pregnancy, dose NS	Tacrolimus, dose NS; prednisone, throughout pregnancy, dose NS	—	—	—	E_3	N_0 S_0	3	—	—
9	El Sebaaly et al. [2007] [Pt 9 of Anderka et al., 2009]	2 g/day until 25 weeks	Prednisone, dose NS; hydroxychloroquine, dose NS	VSD, anterior aorta (possible outlet VSD)	Unk	Unk	E_3	Unk	3	Polydactyly hypoplastic nails	TOP kidney "asymmetry"
10	Perez-Aytes et al. [2008] [Pt 10 of Anderka et al., 2009]	500 mg/day until 10 weeks	Tacrolimus, 12 mg/day	—	Unk Hyper-telorism	M_3	E_3	Unk	6		CL/P chorioretinal coloboma
11	Velinov and Zellers [2008] [Pt 11 of Anderka et al., 2009]	1 g/day for first 8 weeks	Adalimumab, 40 mg every other week.	—	O_0	M_3	E_3	N_0 S_0	6	Brachydactyly	CP only

(Continued)

12	Schoner et al. [2008] [Pt 12 of Anderka et al., 2009]	500–1,500 mg/day until 8 weeks	Cyclophosphamide, 800 mg, schedule NS; azathioprine, 100 mg/day	Truncus arteriosus ARSCA	O_3	M_3	E_3	Unk	9	Hemivertebrae, scoliosis, rib defect	TOP CL/P; facial cleft; coloboma of iris, retina; ACC; esophageal atresia; left renal agenesis; SUA
13	Ang et al. [2008] [Pt 13 of Anderka et al., 2009]	1 g/day for 4 days during 5th week	—	—	O_0	M_1	E_2	N_0 S_0	3	—	Coloboma iris, chorioretinal
14	Andrade Vila et al. [2008] [Pt 14 of Anderka et al., 2009]	1.5 g/day until 5 weeks; 500 mg/day until delivery	Tacrolimus, 6 mg/day; prednisone, 5 mg/day	Mild valvar PS	Unk	Unk	E_{2-3}	Unk	Min 2	—	CP
15	Huang et al. [2008]	2 g/day until 12 weeks	Prednisolone, 30 mg/day; hydroxychloroquine, 200 mg/day; irbesartan, 150 mg/day, started at 12 weeks; felodipine, 5 mg/day	—	O_3	M_3	E_3	Unk	9	—	TOP "Treacher-Collins-like" severe, Bifid nose
16	Parisi et al. [2009]; [Case 3 of Sifontis et al., 2006; Pt 6 of Anderka et al., 2009]	500 mg/day	Tacrolimus, 5 mg/day; prednisone, 5 mg/day; amlodipine, dose NS; metoprolol, dose NS; furosemide, dose NS; epoetin alfa, dose NS; acyclovir, dose NS, first month of pregnancy	ARSCA, ASD2	O_0	M_1	E_3	Unk	4	Bifid vertebrae, short thumbs, fifth fingers, and nails	CP left Bochdalek CDH, TEF, SUA; hypopigmented irides; hypoplastic nipples
17	Jackson et al. [2009]	2 g/day until 17 weeks; 1 g/day until delivery.	Tacrolimus, 10 mg/day; prednisone, 5 mg/day; bactrim, 1.6 g/day, started at 27 weeks; acyclovir, 800 mg/day started prior to 27 weeks	DORV, transposed aorta; valvar PS mitral stenosis TAPVR	O_{3L}	M_3	E_3	Unk	9	Overlapping fingers, vertebral thoracic defects, rib fusion defects	CL/P coloboma, immature white matter, malrotation
18	Dei Malatesta et al. [2009]	500 mg/day	Tacrolimus, 4 mg/day; prednisone, 5 mg/every other day	—	O_1	M_1 MRI lat., Figure 2	E_0	N_0	2	—	Choroidal coloboma with orbital cyst
19	Koshy et al. [2010]	500 mg/day	Tacrolimus, 4 mg/day; prednisone, 10 mg/day; labetolol, 400 mg/day	—	O_0	M_1	E_2	Unk	3	—	Bifid uvula
20	Klieger-Grossman et al. [2010] [Case 1]	750 mg/day, 0–42 weeks	None reported	—	—	—	—	—	0	—	At 4 years, no malformations; normal development
21	Klieger-Grossman et al. [2010] [Case 2]	250 mg twice a day, 8–13 weeks	None reported	—	—	—	—	—	0	—	At 1 year, no malformations; normal development
22	Klieger-Grossman et al. [2010] [Case 7]	500 mg twice a day, 0–6 weeks	None reported	—	—	—	—	—	0	—	At 7 years, no malformations; normal development
23	Klieger-Grossman et al. [2010] [Case 9]	500 mg twice a day, 0–6 weeks	None reported	—	—	—	—	—	0	—	At 1 year, no malformations; normal development
24	Klieger-Grossman et al. [2010] [Case 10]	500 mg/day, 0–7 weeks	None reported	—	—	—	—	—	0	—	Age N.S., no malformations; normal development

TABLE I. (*Continued*)

Total cases 24	Number of cases: Between 5 and 12 weeks, includes continuous use: 15 (62%); mostly <5 weeks: 5 (21%) NS: 4 (17%)	Additional medication 18/24 (75%)	Total CHD = 8 (33%); conotruncal or aortic arch 6/8 (75%)	Unk: 2 (8%); 0: 5 (21%); 1–2: 4 (17%); 3–4: 6 (25%); 5-7: 4 (17%) 9: 3 (12%)	—

Table and selected cases adapted from Anderka et al. [2009].
—, none reported; ACC, agenesis of the corpus callosum; ARSCA, aberrant right subclavian artery; ASD2, atrial septal defect, secundum type; ATG, anti-thymocyte globulin; CDH, congenital diaphragmatic hernia; CHD, congenital heart defect; CL/P, cleft lip/palate; DORV, double outle right ventricle; IVC, inferior vena cava; min, minimum score based on single anomaly reported; MMF, mycophenolate mofetil; NRGA, normally related great arteries; NS, not stated; PS, pulmonic stenosis; SUA, single umbilical artery; TAPVR, total anomalous pulmonary venous return; TEF, tracheo-esophageal fistula; TOP, termination of pregnancy; Unk, unknown; VSD, ventricular septal defect.
[a]Adapted from Vento et al. [1991]; Gougoutas et al., [2007]. Orbit, O_0 normal—O_3 abnormal size and position; Mandible, M_0 normal—M_3 complete absence; Ear, E_0 normal—E_3 severe microtia; Facial nerve, N_0 no involvement—N_3 All branches involved; S_0 no soft tissue hypoplasia—S_3 severe soft tissue deficiency.

bilateral microtia/anotia with micrognathia may be seen with bilateral HFM. Study of MMF teratogenicity may, therefore, hold a clue for elucidation of the etiology of HFM.

With increased reporting and awareness, we suggest that MMF embryopathy will likely become a truly recognizable phenotype. It was suspected in the differential diagnosis of a fetus with known MMF exposure who had severe micrognathia, bifid nasal tip, and bilateral microtia detected by detailed three dimensional ultrasonography [Huang et al., 2008]; these authors also considered Treacher Collins syndrome or another first pharyngeal arch type syndrome. Our patient was diagnosed based on photographic review alone without prior knowledge of the drug exposure or maternal history.

Patients with MMF embryopathy may resemble other syndromes which have malformations involving structures derived from the first and second pharyngeal arches [Passos-Bueno et al., 2009; Heike and Hing, 2010]. The pattern of CHDs suggests that MMF exposure may additionally affect the third and fourth arches, and may be viewed as a neurocristopathy because of the presence of retinal coloboma, midline clefts, hypertelorism, and sensorineural hearing loss. Further evidence to support the hypothesis that MMF embryopathy is a neurocristopathy might be found if thymic defects and/or T-cell deficiency, or minor anomalies such as *heterochromia irides* or white forelock were observed in future patients.

The severity of microtia has prompted caregivers to obtain CT scans of inner ear structures which were normal in a well-studied Spanish girl [Perez-Aytes et al., 2008] and Scottish girl [Ang et al., 2008]. Unlike the CHARGE syndrome [Amiel et al., 2001] and the branchio-oculo-facial syndrome [Tekin et al., 2009; Stoetzel et al., 2009; Milunsky et al., 2010] in which semi-circular canal and temporal bone anomalies, respectively, have a strong association with both the pinna malformation and gene mutation, it is too soon to know if there is a relationship between outer ear and inner ear anomalies in MMF embryopathy. Additional patients must be studied; inner ear evaluation on our patient is currently pending.

Our study does not address the challenge of estimating the absolute risk to the fetus. Using the Organization of Teratology Information Specialists network, Klieger-Grossman et al. [2010] found no malformations in five livebirths out of 10 reported pregnancies exposed to MMF.

We propose that patients suspected of having one or more defects associated with MMF exposure should be viewed as having a potential multiple malformation syndrome, even when there is only an apparent isolated defect. In addition to a meticulous surface examination with attention to measuring growth parameters, especially the head circumference, we suggest including an echocardiogram, due to the frequent occurrence of CHDs after MMF exposure. The skin tags in our patient may be the first report in MMF embryopathy, and should be sought in future cases, or when previously diagnosed cases are re-examined. The echocardiogram should be performed under the direction of a pediatric cardiologist so that aortic arch defects can be sought, and complex CHDs can be accurately defined. For the majority of MMF-exposed children with microtia, consideration should be given to CT scanning of inner ear structures. A formal eye examination is needed with the greatest attention to the posterior chamber.

Future clinical genetic research about MMF exposure will focus on identifying pregnancies at risk, careful clinical examination of

external features, identifying potentially asymptomatic anomalies, and attempts to obtain follow-up for natural history.

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REFERENCES

Amiel J, Attieé-Bitach T, Marianowski R, Cormier-Daire V, Abadie V, Bonnet D, Gonzales M, Chemouny S, Brunelle F, Munnich A, Manach Y, Lyonnet S. 2001. Temporal bone anomaly proposed as a major criteria for diagnosis of CHARGE syndrome. Am J Med Genet 99:124–127.

Anderka MT, Lin AE, Abuelo DN, Mitchell AA, Rasmussen SA. 2009. Reviewing the evidence for mycophenolate mofetil as a new teratogen: Case report and review of the literature. Am J Med Genet Part A 149A:1241–1248.

Andrade Vila JH, da Silva JP, Guilhen CJ, Baumgratz JF, da Fonseca L. 2008. Even low dose of mycophenolate mofetil in a mother recipient of heart transplant can seriously damage the fetus. Transplantation 86:369–370.

Ang GS, Simpson SA, Reddy AR. 2008. Mycophenolate mofetil embryopathy may be dose and timing dependent. Am J Med Genet Part A 146A:1963–1966.

Armenti VT, Radomski JS, Moritz MJ, Gaughan WJ, Hecker WP, Lavelanet A, McGrory CH, Coscia LA. 2004. Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. In: Cecka JM, Terasaki PI, editors. Clinical transplants 2004. Los Angeles, CA: UCLA Immunogenetics Center. pp. 103–114.

Carey JC. 2008. Where observation is concerned, chance favors only the prepared mind. Obstet Gynecol 111:479–480.

Dei Malatesta MF, Rocca B, Gentile T, Hadjistilianou M, Borri M, de Francesco S, Pisani F, Famulari A. 2009. A case of coloboma in a newborn to a woman taking mycophenolate mofetil in pregnancy after kidney transplantation. Transplant Proc 41:1407–1409.

El Sebaaly Z, Charpentier B, Snanoudj R. 2007. Fetal malformations associated with mycophenolate mofetil for lupus nephritis. Nephrol Dial Transplant 22:2722.

Heike CL, Hing AV. 2010. Craniofacial microsomia overview. GeneReviews. Posted March 19, 2009. Accessioned September 9, 2010.

Horgan JE, Padwa BL, LaBrie RA, Mullken JB. 1995. OMENS-Plus: analysis of craniofacial and extracraniofacial anomalies in hemifacial microsomia. Cleft Palate Craniofac J 32:405–412.

Huang SY, Chueh HY, Shaw SW, Shih JC, Cheng PJ. 2008. Sonographic diagnosis of fetal malformations associated with mycophenolate mofetil exposure in utero. Am J Obstet Gynecol 199:e6–e8.

Hunter A, Frias JL, Gillessen-Kaesbach G, Hughes H, Jones KL, Wilson L. 2009. Elements of morphology: Standard terminology for the ear. Am J Med Genet Part A 149A:40–60.

Jackson P, Paquette L, Watiker V, Randolph L, Ramanathan R, Seri I. 2009. Intrauterine exposure to mycophenolate mofetil and multiple congenital anomalies in a newborn: Possible teratogenic effect. Am J Med Genet Part A 149A:1231–1236.

Källén B, Westgren M, Aberg A, Olausson OP. 2005. Pregnancy outcome after maternal organ transplantation in Sweden. Br J Obstet Gynaecol 112:904–909.

Klieger-Grossman C, Chitayat D, Lavign S, Kao K, Garcia-Bournissen F, Quinn D, Luo V, Sermer M, Riordan S, Laskein C, Matok I, Gorodischer R, Chambers C, Levi A, Koren G. 2010. Prenatal exposure to mycophenolate mofetil: An updated estimate. JOGC 32:794–797.

Koshy AN, Strong D, Earles G, Fassett RG. 2010. Congenital malformations with low-dose mycophenolate mofetil after kidney transplantation. Nephrology 15:133–135.

Lammer EJ. 1991. Preliminary observations on isoretinoin-induced ear malformations and pattern formation of the external ear. J Craniofac Genet Dev Biol 11:292–295.

Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. 2004. Mycophenolate mofetil in pregnancy after renal transplantation: A case of major fetal malformations. Obstet Gynecol 103:1091–1094.

Lin AE, Belmont J, Ghaffar S. 2006. The heart. In: Stevenson RE, Hall JG, editors. Human malformations and related anomalies, 2nd edition. New York: Oxford University Press. pp. 85–120.

Merlob P, Stahl B, Klinger K. 2009. Tetrada of the possible mycophenolate mofetil embryopathy: A review. Repro Toxicol 28:105–108.

Milunsky JM, Maher TM, Zhao G, Wang Z, Mulliken JB, Chitayat D, Clemens M, Stalker HJ, Bauer M, Burch M, Chénier S, Cunningham ML, Drack AV, Janssens S, Karlea A, Klatt R, Kini U, Klein O, Lachmeijer AM, Megarbane A, Mendelsohn NJ, Meschino WS, Mortier GR, Parkash S, Ray CR, Roberts A, Roberts A, Reardon W, Schnur RE, Smith R, Splitt M, Tezcan K, Whiteford ML, Wong DA, Zori R, Lin AE. 2010. Genotype–phenotype analysis of the branchio-oculo-facial syndrome. Am J Med Genet A 155A:22–32.

Obler D, Juraszek AL, Smoot LB, Natowicz MR. 2008. Double outlet right ventricle: Aetiologies and associations. J Med Genet 45:481–497.

Parisi MA, Zayed H, Slavotinek AM, Rutledge JC. 2009. Congenital diaphragmatic hernia and microtia in a newborn with mycophenolate mofetil (MMF) exposure: Phenocopy for Fryns syndrome or broad spectrum of teratogenic effects? Am J Med Genet Part A 149A: 1237–1240.

Passos-Bueno MR, Ornelas CC, Fanfaniello RD. 2009. Syndromes of the first and second pharyngeal arches: A review. Am J Med Genet Part A 149A:1853–1859.

Perez-Aytes A, Ledo A, Boso V, Saenz P, Roma E, Poveda JL, Vento M. 2008. In utero exposure to mycophenolate mofetil: A characteristic phenotype? Am J Med Genet Part A 146A:1–7.

Pérgola PE, Kancharla A, Riley DJ. 2001. Kidney transplantation during the first trimester of pregnancy: Immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone. Transplantation 71: 994–997.

Schoner K, Steinhard J, Figiel J, Rehder H. 2008. Severe facial clefts in acrofacial dystosis: A consequence of prenatal exposure to mycophenolate mofetil? Obstet Gynecol 111:483–486.

Sifontis NM, Coscia LA, Constantinescu S, Lavelanet A, Moritz MJ, Armenti VT. 2006. Pregnancy outcomes in solid organ transplant with exposure to mycophenolate mofetil or sirolimus. Transplantation 82: 1698–1702.

Stoetzel C, Riehm S, Bennouna Greene V, Pelletier V, Vigneron J, Leheup B, Marion V, Hellé S, Danse JM, Thibault C, Moulinier L, Veillon F, Dollfus H. 2009. Confirmation of *TFAP2A* gene involvement in branchio-oculo-facial syndrome (BOFS) and report of temporal bone anomalies. Am J Med Genet A 149A:2141–2146.

Tekin M, Sirmaci A, Yüksel-Konuk B, Fitoz S, Sennaroğlu L. 2009. A complex TFAP2A allele is associated with branchio-oculo-facial syndrome and inner ear malformation in a deaf child. Am J Med Genet A 149A:427–430.

Tjeertes IF, Bastiaans DE, van Ganzewinkel CJ, Zegers SH. 2007. Neonatal anemia and hydrops fetalis after maternal mycophenolate mofetil use. J Perinatol 27:62–64.

Velinov M, Zellers N. 2008. The fetal mycophenolate mofetil syndrome. Clin Dysmorphol 17:77–78.

Vento RA, LaBrie RA, Mulliken JB. 1991. The O.M.E.N.S. classification of hemifacial microsomia. Cleft Palate Craniofac J 28:68–76.

Vento M, Perez-Aytes A, Ledo A, Boso V, Carey JC. 2008. Mycophenolate mofetil during pregnancy: Some words of caution. Pediatrics 122: 184–185.