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Editor's Note

In this article Jackson and colleagues add another well documented patient with the mycophenolate mofetil embryopathy. This report, along with the ensuing paper by Anderka et al., bring the total number of cases of the syndrome to 14, most published in the last two years. A third paper in this issue of the Journal by Parisi and colleagues describes in detail one of the original patients reported only in tabular form in a previous summary of cases. While the evidence for teratogenicity here is almost entirely clinical (and not experimental or epidemiologic);, it is—as these papers demonstrate—compelling.

John C. Carey, MD
Editor-in-Chief

Intrauterine Exposure to Mycophenolate Mofetil and Multiple Congenital Anomalies in a Newborn: Possible Teratogenic Effect

Paige Jackson,[1]* Lisa Paquette,[1] Valerie Watiker,[2] Linda Randolph,[2] Rangasamy Ramanathan,[1] and Istvan Seri[1]

[1]Center for Fetal and Neonatal Medicine, USC Division of Neonatal Medicine, Department of Pediatrics, Childrens Hospital Los Angeles, Women's and Children's Hospital of the LAC/USC Medical Center, Keck School of Medicine, University of Southern California, Los Angeles, California

[2]Division of Medical Genetics, Department of Pediatrics, Childrens Hospital Los Angeles, Women's and Children's Hospital of the LAC/USC Medical Center, Keck School of Medicine, University of Southern California, Los Angeles, California

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There is very little data linking the use of immunomodulating agents following solid organ transplantation in pregnant women with specific congenital anomalies in the offspring. Here we report on a late preterm infant with multiple, nonsyndromic, congenital anomalies including microtia/anotia, cleft lip and palate, micrognathia, ocular hypertelorism, microphthalmia and cataracts, complex congenital heart disease, rib anomalies, and intestinal malrotation. The similarity of the complex anomalies in our case to other reported cases suggests that the abnormalities are likely due to mycophenolate mofetil alone or in combination with other immunosuppressive medications taken by the mother during pregnancy. © 2009 Wiley-Liss, Inc.

Key words: teratogenicity; mycophenolate mofetil; multiple congenital anomalies; microtia/anotia; cleft lip/palate; double-outlet right ventricle

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INTRODUCTION

An increasing number of women of childbearing age have had solid organ transplantation and are taking multiple immunosuppressive medications to decrease the risk of organ rejection. The new generation of immunomodulators is indeed more effective at helping patients accept and maintain transplanted solid organs [European Mycophenolate Mofetil Cooperative Study Group 1995; Sollinger et al., 1995]. However, very little information is available on the possible teratogenicity of the medications frequently used in transplant patients. It has been reported that, although more than

*Correspondence to:
Paige Jackson, M.D., Center for Fetal and Neonatal Medicine, USC Division of Neonatal Medicine, Childrens Hospital Los Angeles, 4650 Sunset Blvd, MS #31, Los Angeles, CA 90027.
E-mail: pjackson@chla.usc.edu
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70% of post-transplant pregnancies result in live birth, 30–50% of these live births have reported complications [Armenti et al., 1999]. Among the complications, rare cases of congenital anomalies in infants born to mothers after solid organ transplantation have been reported to national transplant registries. Mycophenolate mofetil (MMF) is a newer generation immunosuppressant used to prevent rejection of transplanted organs as well as for the treatment of autoimmune disorders. Its use for immunosuppression after solid organ transplantation has increased from 11.9% in 1995 to 74.6% in 2004 [Pergola et al., 2001; Le Ray et al., 2004]. MMF is a reversible inhibitor of inosine monophosphate dehydrogenase and thus inhibits de novo purine synthesis necessary for T and B lymphocyte proliferation [Pergola et al., 2001].

Studies of MMF in animals have reported teratogenicity at significantly *lower* doses than those routinely used in human adults. Pregnant rats and rabbits treated with MMF have exhibited intrauterine death, anophthalmia, agnathia, hydrocephalus, and diaphragmatic hernia [Sifontis et al., 2006]. As a result of the findings of animal studies, previously reported human cases and data from the US National Transplant Pregnancy Registry (NTPR), MMF was advanced from FDA pregnancy category C to category D in October 2007. With this change, the FDA acknowledged that the use of MMF in pregnant women is "clearly associated with some health risks" to the fetus [USFDA, 2007].

Here we report on a female infant with multiple congenital anomalies. Based on the constellation of the findings and the data in the literature, we propose that these anomalies are likely due to MMF alone or in combination with other medications taken during the pregnancy.

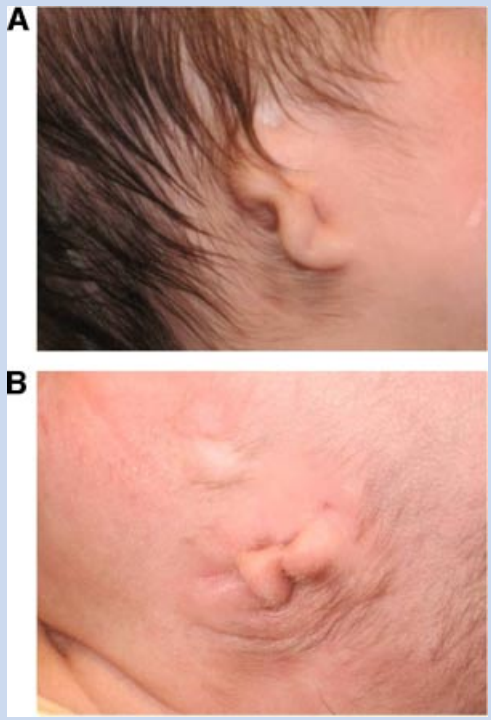

FIG. 1. A and B: Bilateral microtia and external ear canal atresia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

CASE REPORT

The female patient was born at 35 weeks gestation to a 20-year-old G_1P_1 mother who had received a liver transplantation for autoimmune hepatitis-associated liver failure 18 months prior to delivery. She had been receiving the following immunosuppressants, MMF (1,000 mg BID), tacrolimus (5 mg BID), and prednisone (2.5 mg BID). Once the pregnancy was recognized at 17 weeks, MMF was decreased to 500 mg BID, and the other medications were unchanged. All prenatal serologies were normal. Maternal history was negative for use of alcohol, tobacco, or illicit drugs. At 17 weeks, prenatal vitamins and folic acid were added to the maternal regimen. Bactrim (800 mg BID) and Acyclovir (400 mg BID) were started for infection prophylaxis prior to 27 weeks gestation.

At 18 weeks' gestation, the fetus was noted to have bilateral cleft lip and palate. At 23 weeks' gestation, detailed fetal echocardiography revealed that the fetus had a double-outlet right ventricle with mitral stenosis, anterior and rightward aorta with mild valvular pulmonary stenosis, and moderate hypoplasia of the left ventricle. Amniocentesis revealed normal chromosomes (46,XX), and a negative fluorescence in situ hybridization (FISH) for 22q11.2. The prenatal findings of the complex congenital heart disease and cleft anomalies were confirmed at delivery (Figs. 1A,B and 2A,B). Additional postnatal findings were cataracts, left microphthalmia with ocular hypertelorism (Fig. 2B), microtia with external ear canal atresia (Fig. 1A,B), intestinal malrotation, overlapping fingers (Fig. 2A), segmental anomalies of the T2–T5 vertebral bodies, and fusion of the 4th and 5th ribs on the right and 3rd, 4th, and 5th ribs on the left. High-resolution chromosomes and comparative genomic hybridization microarray were normal.

The patient's postnatal course was notable for significant cardiorespiratory and gastrointestinal complications. Although the patient's head ultrasound was normal, brain MRI revealed immature white matter development, focal white matter necrosis, and bilateral coloboma malformations. The patient developed significant pulmonary overcirculation with systemic steal shortly after delivery due to the underlying complex heart disease, and underwent emergent pulmonary artery banding and PDA ligation on postnatal day #4. Further palliative cardiac surgeries were considered for the future. Thereafter, she presented with significant feeding intolerance and was diagnosed with intestinal malrotation without volvulus. She underwent intestinal malrotation repair with a Ladd's procedure, appendectomy, and placement of a gastrostomy tube on postnatal day #33. Following this and all subsequent surgeries, her postoperative course was complicated by the development of pulmonary hypertensive crises of varying severity.

Because of her left microphthalmia and bilateral corneal opacities, the patient underwent right corneal transplant on postnatal day #54 with removal of sutures on postnatal day #63. A tracheostomy tube was placed on postnatal day #86 secondary to persistent severe respiratory distress. On postnatal day #112, the patient was diagnosed with pneumonia. Despite aggressive respiratory support and treatment with broad-spectrum antibiotics, the patient's respiratory and cardiovascular status continued to worsen. On

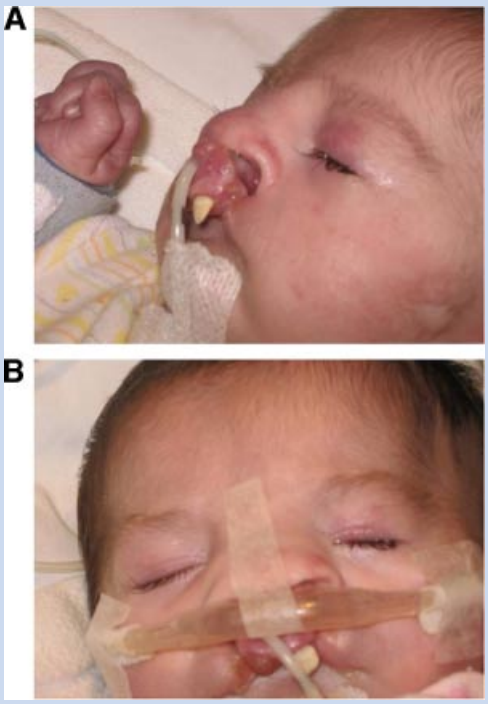

FIG. 2. A and B: Bilateral cleft lip, central incisor, overlapping fingers, hypertelorism, and left microphthalmia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

postnatal day #124, after repeated discussions with the family the decision was made not to escalate provision of intensive care, and the next day, the patient expired secondary to cardiorespiratory failure. Autopsy was declined.

DISCUSSION

Previously, there have been 10 cases of infants exposed to MMF reported in the literature [Vento et al., 2008]. Two additional cases were reported in early 2008. The severity of the cases ranges from mild to quite severe. The initial case to report a fetal abnormality in a mother treated with MMF noted hypoplastic nails and brachydactyly in an otherwise normal infant [Pergola et al., 2001]. Subsequently, over the next several years, a pattern of malformations seemed to be emerging in infants exposed to MMF during the critical organogenesis period, which included significant external ear abnormalities and facial clefting. Table I summarizes the anomalies reported to be associated with intrauterine exposure to MMF alone or in combination with other immunomodulators.

The findings in our patient included microtia/anotia, cleft lip and palate, micrognathia, ocular hypertelorism, microphthalmia and cataracts, complex congenital heart disease, vertebral and rib anomalies, and intestinal malrotation. Among these findings, vertebral and rib anomalies and intestinal malrotation have not been reported previously (Table I).

Including our case, microtia appears to lead the list of congenital abnormalities noted in these infants. Cleft lip/palate and complex congenital heart disease were also noted in the majority of cases previously reported in the literature. Ocular hypertelorism, micrognathia, and renal abnormalities were also common findings. Eye abnormalities, tracheal abnormalities, and abnormal digits/nails were noted in a few cases, though sporadically. Finally, there were many other abnormalities seen in isolated cases only. Only one group followed their patient long enough to be able to describe developmental delay in their case report [Velinov and Zellers, 2008]. Neuro-developmental follow-up in this particular patient was documented at 20 months.

Table II describes the intrauterine immunomodulator medication exposure in our case and the 12 cases previously reported in the literature. All of the cases have MMF exposure in common. Almost all of the mothers, however, were also on additional medications as part of a regimen for graft rejection prophylaxis, treatment for autoimmune disease, or treatment for other pre-existing conditions. The most common secondary medications were tacrolimus and prednisone as the majority of cases were exposed to one or both of these medications in addition to MMF. However, the involvement of prednisone is less likely in the development of the congenital anomalies as infants are (at least partially) protected from the potential untoward effects of prednisone exposure due to placental inactivation of this steroid medication. Indeed, prednisone has not been reported to have teratogenic activity in humans at therapeutic doses [OPTN, 2006]. A small number of cases were also exposed to azathiaprine. However, it is unlikely that these malformations, occurring with medication exposure during organogenesis, are due to azathiaprine, as the placenta does not produce the enzyme necessary for converting azathiaprine to its active metabolite [OPTN, 2006]. One case also had fetal exposure to cyclophosphamide, in addition to MMF and azathiaprine [Schoner et al., 2008]. Studies on cyclophosphamide exposure have shown teratogenicity manifesting as cleft palate, abnormal digits, and hypoplastic nails if the drug is taken during the critical period of organogenesis [OPTN, 2006]. Finally, several medications were grouped into the ''other medications'' category depicted in Table II. These medications were given for a variety of concomitant conditions and include olanzapine, nitrazepam, diazepam, haloperidol, darbepoetin alfa-methyldopa, hydroxychloroquine, perindopril, pravastatin, diltiazen, carbamazepine, and adalimumab.

Interestingly, several other medications cause a similar presentation to that of the proposed MMF embryopathy. Retinoic acid exposure during organogenesis has previously been shown to cause complex congenital heart malformations, cleft palate, microtia, and ocular hypertelorism [Loureiro et al., 2005]. The fetal hydantoin syndrome, caused by in utero exposure to diphenylhydantoin, is also associated with congenital heart disease and cleft palate [Holmes et al., 2001]. In addition, multiple anticonvulsants are associated with digital anomalies such as nail hypoplasia [Guven et al., 2006]. There is no history of our patient being exposed to any of these medications, though it is possible to hypothesize a similar pathogenesis.

Timing of exposure is also important in determining teratogenicity. Each of the infants discussed previously was exposed to MMF during the critical organogenesis period. The total timing of the exposure ranged from only 4 days during the seventh week of gestation to the entire duration of the pregnancy. The actual dosing ranged from 500 to 2,000 mg/day. The malformation patterns

TABLE I. Summary of Abnormalities Associated With Intrauterine Exposure to MM Alone or in Combination With Other Immunomodulators

Anomalies	Ang et al.	Andrade	Pergola et al.	LeRay et al.	Perez-Aytes	Velinov et al.	Tjeertes et al.	Schoner et al.	El Sebaaly	Sifontis et al., Case #2	Sifontis et al., Case #3	Sifontis et al., Case #4	This report
Agenesis CC				X				X					
Microtia/anotia	X	X		X	X	X	X	X	X	X	X	X	X
Hypertelorism				X	X	X							X
Cataracts								X					X
Microphthalmia		X											X
Chorioretinal Coloboma	X				X			X					
Ptosis					X								
Epicathal folds						X							
Cleft lip/palate		X		X	X	X		X		X	X		X
Micrognathia				X	X			X					X
Tracheomalacia/TEF						X		X					
CDH											X		
Thymic hypoplasia								X					
CHD								X	X		X	X	X
Intestinal malrotation													X
Umbilical hernia		X											
Renal abnormalities				X				X	X			X	
Brachydactyly			X			X							
Polydactyly									X			X	
Hypoplastic nails			X						X			X	
Vertebral/rib anomalies													X
Anemia							X						
Nonimmune hydrops							X						
Developmental delay						X							

CHD, Congenital heart disease; CC, corpus callosum; TEF, tracheoesophageal fistula; CDH, congenital diaphragmatic hernia.

TABLE II. In Utero Medication Exposure in the Literature in Pregnancies of Mothers Following Solid Organ Transplantation and Auto-Immune Disorders

	MM	Tacrolimus	Sirolimus	Prednisone	Azathio-prine	Cyclophos- phamide	Other medications
This report	X	X		X			
LeRay et al.	X	X		X	X		
Perez-Aytes et al.	X	X					
Velinov et al.	X						X
Tjeertes et al. [2007]	X			X			
Schoner et al.	X				X	X	X
El Sebaaly et al.	X						
Sifontis et al. 2	X	X	X	X			
Sifontis et al. 3	X	X		X			
Sifontis et al. 4	X	X		X			
Pergola et al.	X	X		X			X
Ang et al. [2008]	X						
Andrade Vila et al. [2008]	X	X		X			X

between the three cases exposed to the highest dosing regimen of MMF varied widely, ranging from hypoplastic nails and minor digit abnormalities to the full spectrum of congenital anomalies including microtia, congenital heart disease, and renal abnormalities, in addition to the nail and digit abnormalities [Pergola et al., 2001; Sifontis et al., 2006; El Sebaaly et al., 2007]. All of these infants were noted to be exposed to MMF at 2 g/day until well into the second trimester. Interestingly, the infants exposed to the smallest doses of MMF during organogenesis all were noted to have the significant external ear abnormalities and cleft lip/palate common to the majority of infants reported [Le Ray et al., 2004; Sifontis et al., 2006 (case 3); Perez-Aytes et al., 2008]. At this time, it is difficult to speculate which dosing regimen provides the higher risk for congenital abnormalities (Table III).

As mentioned earlier, the FDA now has much more stringent guidelines for the use of MMF in pregnant women and those of childbearing age. As of September 2007, the FDA has included specific warnings regarding the potential teratogenic effects of MMF if used during pregnancy, especially during the critical organogenesis period [Carey, 2008]. In addition, the manufacturer now recommends effective contraception before, during, and 6 weeks after MMF therapy.

CONCLUSION

As our patient exhibited some of the same anomalies as previously described in fetuses exposed to MMF, it is likely that this immunomodulator was teratogenic in our case as well. It is impossible to determine if the anomalies not previously reported for MMF (microphthalmia, rib anomalies, and intestinal malrotation) resulted from the embryotoxic effect of MMF, the other maternal medications or a specific combination or dosing regimen of all of the medications the mother was exposed to. Specific counseling about the potential risks and thorough

TABLE III. Dosing and Timing of Medication Exposure

Author	MMF daily dose	GA started	Gestational age discontinued
Our case	2,000 mg	0 weeks	17 weeks
	1,000 mg	17 weeks	35 weeks
Ang et al.	1,000 mg	7 weeks	7 weeks
Pergola	2,000 mg	6 weeks	26 weeks
	1,000 mg	26 weeks	34 weeks
Leray	500 mg	0 weeks	13 weeks
Perez-Aytes	500 mg	0 weeks	10 weeks
Velinov	1,000 mg	0 weeks	8 weeks
Tjeertes et al.	?	0 weeks	35 weeks
Schoner	1,500 mg	0 weeks	8 weeks
El Sebaaly	2,000 mg	0 weeks	25 weeks (termination)
Sifontis 2	1,000 mg	0 weeks	24 weeks
Sifontis 3	500 mg	0 weeks	Term
Sifontis 4	2,000 mg	0 weeks	13 weeks
Andrade	1,000 mg	0 weeks	5 weeks
	500 mg	5 weeks	Term

evaluation of the fetus and newborn is essential if exposure to MMF alone or in combination to other immunomodulators occurs. In particular, a detailed examination for ophthalmic and auricular anomalies, cleft lip and palate, and cardiac anomalies in the fetus exposed to MMF should be considered.

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