American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 523-526
DOI: 10.12659/AJCR.908433

Received: 2017.12.07
Accepted: 2018.02.07
Published: 2018.05.03

Congenital Esophageal Atresia and Microtia in a Newborn Secondary to Mycophenolate Mofetil Exposure During Pregnancy: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCEF 1 Musaed Mohammed Alsebayel
ADE 2,3 Faisal Abdulrahman Abaalkhail
BE 1 Faisal Mohammed Alsebayel
BDE 4 Dema A. Alissa
BDE 3,4 Ahmed Hamdan Al-Jedai
ADEF 2,3 Hussien Elsiesy

1 College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
2 Department of Liver and Small Bowel Transplantation and Hepatobiliary-Pancreatic Surgery, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
3 College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
4 Pharmaceutical Care Divisions, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Corresponding Author: Musaed Mohammed Alsebayel, e-mail: Msa3dalsebayel@gmail.com
Conflict of interest: None declared

Patient: Female, 20
Final Diagnosis: Esophageal atresia
Symptoms: Cough • gagging • poor feeding
Medication: Mycophenolate mofetil
Clinical Procedure: Esophageal repair
Specialty: Transplantology

Objective: Congenital defects/diseases

Background: Mycophenolate mofetil (MMF) is one of the most commonly prescribed drugs to prevent organ transplant rejection in combination with calcineurin inhibitors and steroids. It has a different toxicity profile than tacrolimus and cyclosporine. Gastrointestinal tract disturbances are the most common adverse effects. The use of MMF in pregnant women, however, holds great risk of miscarriage and fetal development defects such as external ear malformation, ocular anomalies, cleft lip and palate, and abnormality of distal limbs, heart, esophagus, and kidneys. Based on post-marketing studies, its pregnancy category was reclassified as category D by the US FDA in 2007.

Case Report: A 20-year-old woman received a deceased-donor liver transplant for end-stage liver disease secondary to autoimmune hepatitis. She had 3 miscarriages while on MMF. In her fourth pregnancy she was exposed to MMF in the first trimester, which was stopped by week 20 of the pregnancy. Obstetric ultrasound suggested a cephalic presentation fetus with abdominal circumference. Her pregnancy resulted in an infant with tracheoesophageal fistula, esophageal atresia, and a bilateral ear canal atresia (microtia) with normal sensorineural conduction. There were no other congenital abnormalities. Thoracoscopic ligation of fistula and thoracotomy with esophageal repair were performed and a bone-anchored hearing aid for conductive hearing loss was implanted. Here, we report a case of congenital esophageal atresia and microtia secondary to mycophenolate mofetil.

Conclusions: MMF should be avoided during pregnancy. Transplanted female patients of reproductive age should receive appropriate counseling.

MeSH Keywords: Congenital Abnormalities • Esophageal Atresia • Teratogens

Abbreviations: **BW** – boxed warning; **FDA** – Food and Drug Administration; **HBcAb** – hepatitis B core antibody; **IMPDH** – inosine monophosphate dehydrogenase; **KFSH&RC** – King Faisal Specialist Hospital and Research Center; **MMF** – mycophenolate mofetil; **NTPR** – National Transplantation Pregnancy Registry

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/908433

1028 — 2 18

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Mycophenolate mofetil (MMF; CellCept®) is one of the most commonly prescribed immunosuppressant drugs used to prevent organ transplant rejection [1]. In the United States, 89.9% of *de novo* renal transplant recipients are prescribed MMF or other mycophenolic acid derivatives, making it the most used immunosuppressant in these patients [2]. MMF inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), which plays an important role in the *de novo* synthesis of purines, and intercepts the proliferation of B and T lymphocytes [3]. Mycophenolic acid derivatives have a different toxicity profile compared to calcineurin inhibitors and other antiproliferative agents [4]. Gastrointestinal tract disturbances are the most commonly reported adverse effects of MMF, with afebrile diarrhea being the most commonly reported manifestation, with an incidence rate of 12–40% in renal transplant patients [5]. However, the use of MMF for pregnant women has a great risk of miscarriage and fetal development defects such as external ear malformation, ocular malformation, cleft lip and palate, and abnormality of distal limbs, heart, esophagus or kidneys [6–10]. The National Transplantation Pregnancy Registry (NTPR) revealed a 45% miscarriage rate of 33 pregnancies that were reported by 24 patients receiving mycophenolate treatment, and 4–5% congenital defects rate compared to 3% in the general population of the United States [11]. In 2007, MMF was reclassified by the US Food and Drug Administration from class C to class D in response to studies that reported miscarriages and teratogenic effects of MMF products and metabolites [12]. In June 2012, the US FDA added a boxed warning (BW) to the prescribing information of all mycophenolic acid derivatives, describing their potential to cause increased risks of first trimester pregnancy loss and congenital malformations.

Case Report

A 20-year-old woman received a deceased-donor liver transplant secondary to autoimmune hepatitis in 2001 that resulted in liver cirrhosis and end-stage liver failure. The medical record of the patient and her son were retrospectively analyzed after obtaining consent from her and her son and approval of the Research Ethics Committee of King Faisal Specialist Hospital and Research Center (KFSH&RC). Her initial immunosuppression consisted of tacrolimus, prednisolone, and MMF (CellCept®). On September 2006, MMF (CellCept®) was stopped. The donor was hepatitis B core antibody (HbcAb)-positive; therefore, the recipients received lamivudine throughout this period as a prophylaxis for *de novo* hepatitis B infection. Prednisolone was tapered and kept at 5 mg once daily. She attempted pregnancy in 2005, during which she had 2 miscarriages at week 6 of gestation. She also had a third miscarriage in 2006 at the 9th week of gestation. Protein S and C antithrombin III deficiency

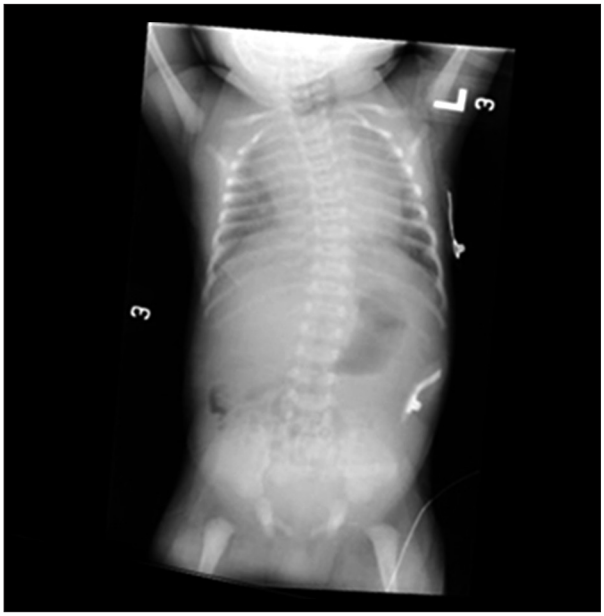

Figure 1. Chest and abdominal X-ray with dilated lower esophagus and stomach and lower tracheoesophageal fistula diagnostic of esophageal atresia.

was diagnosed during her first pregnancy. For her fourth pregnancy, her last menstrual period was on 19 May 2006. During that time, she was on the same immunosuppressive regimen. MMF was stopped on 18 September 2006 (in the 20th week of pregnancy) and the mother was on dual immunosuppression with slight elevation of liver function test, which was managed by increasing tacrolimus dose, aiming for a level of 10 ug/L. At 37 weeks, an obstetric ultrasound was done, which showed a cephalic presentation fetus with abdominal circumference of 35.4 cm (75th centile), a head circumference in the 95th centile, and an estimated fetal weight of 3.827 kg. The fetus scored 8 out of 8 in a biophysical profile and had polyhydramnios with 20 cm of amniotic fluid and an enlarged stomach. A lower-segment C-section was performed at 38 weeks due to failure to progress with full dilatation. The newborn was a male who had a tracheoesophageal fistula with esophageal atresia and a bilateral ear canal atresia (Microtia) with normal sensorineural conduction, with no other congenital abnormalities. Thoracoscopic ligation of fistula and thoracotomy with esophageal repair was performed and a bone anchored hearing aid for conductive hearing loss was implanted. Figure 1 shows plain abdominal and chest X-ray of the newborn diagnostic of esophageal atresia and Figure 2 shows a contrast study after the repair.

Discussion

Mycophenolic acid derivatives have been associated with a specific pattern of congenital anomalies that include microtia,

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

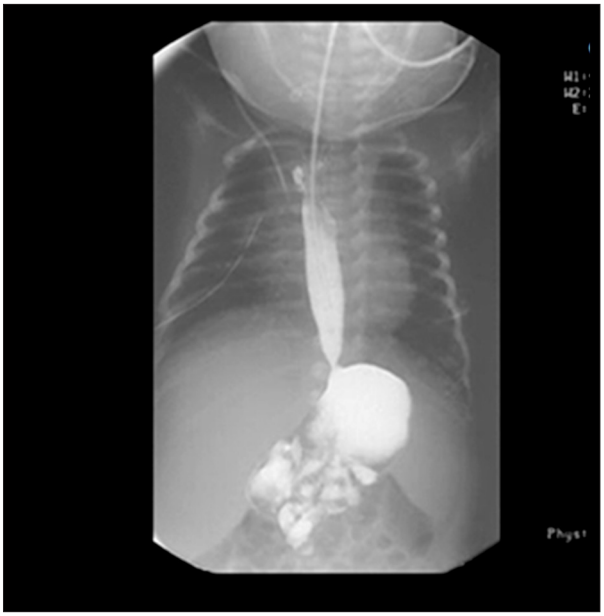

Figure 2. Contrasted study after repair, showing established continuity of the esophagus, and closure of tracheoesophageal fistula without leak or significant stenosis.

cleft lip and palate, external auditory canal atresia, ocular anomalies, diaphragmatic hernia, and congenital heart defects [9–14]. Esophageal atresia associated with prenatal exposure to mycophenolic acid has been described in 9 patients who also had other associated malformations. Hoeltzenbein et al., Schonar et al., and Parisi et al. reported cases of several congenital malformations in which mothers were receiving mycophenolate therapy, among other medications [14–17]. Martin et al. reported 4 cases of esophageal atresia; 2 of these cases matched the proposed embryopathy phenotype (cleft palate and lip, external auditory canal atresia, congenital heart defects, and microtia) [18]. The other 2 cases presented with esophageal atresia with other milder manifestations; one with patent foramen ovale and mild facial anomalies, and the other patient was diagnosed with congenital dorsal hemivertebra. The patients did not show any association between the periods of prenatal exposure to mycophenolic acid and the reported congenital anomalies [13,14].

In our case, the fetus was exposed to MMF until the 20th week of pregnancy. In 2007, Roche Laboratories, Inc. issued a drug warning indicating that MMF use during pregnancy is associated with increased pregnancy loss and congenital malformation, especially external ear and facial malformations, as well as anomalies of distal limbs, heart, esophagus, and kidneys. Based on the post-marketing data and the US National Transplantation Pregnancy Registry, the US FDA changed the MMF pregnancy category from C to D [12]. Since steroids and tacrolimus are not known to cause this pattern of anomalies, the most likely cause is MMF teratogenicity. Our patient had 2 uneventful pregnancies after discontinuation of MMF, while still on steroids, tacrolimus, and lamivudine.

Conclusions

The use of mycophenolic acid derivatives during pregnancy is associated with increased risk of esophageal atresia and microtia. Its use should be avoided in women of reproductive age who are pregnant or planning to get pregnant. Counseling patients about its risk and the importance of contraception and pregnancy planning should be emphasized.

Acknowledgment

We thank the patient who agreed to be the subject of this research paper and her husband, and we are grateful to Mrs. Carla Mercado for expert secretarial support.

Conflict of interest

None.

References:

1. Allison AC, Eugui EM: Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF). Clin Transplant, 1996; 10: 77–84
2. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2010 data report. Am J Transplant, 2012; 12(Suppl. 1): 1–156
3. Ransom JT: Mechanism of action of mycophenolate mofetil. Ther Drug Monit, 1995; 17: 681–84
4. Suthanthiran M, Morris RE, Strom TB: Immunosuppressants: Cellular and molecular mechanisms of action. Am J Kidney Dis, 1996; 28: 159–72
5. De Mattos AM, Olyaei AJ, Bennett WM: Nephrotoxicity of immunosuppressive drugs: Long-term consequences and challenges for the future. Am J Kidney Dis, 2000; 35: 333–46
6. Zachariah MS, Tornatore KM, Venuto RC: Kidney transplantation and pregnancy. Curr Opin Organ Transplant, 2009; 14: 386–91
7. Perez-Aytes A, Marin-Reina P, Boso V et al: Mycophenolate mofetil embryopathy: A newly recognized teratogenic syndrome. Eur J Med Genet, 2017; 60(1): 16–21
8. Dei Malatesta M, Rocca B, Gentile T et al: A case of coloboma in a newborn to a woman taking mycophenolate mofetil in pregnancy after kidney transplantation. Transplant Proc, 2009; 41(4): 1407–9
9. Merlob P, Stahl B, Klinger G: Tetrada of the possible mycophenolate mofetil embryopathy: A review. Reprod Toxicol, 2009; 28: 105–8
10. Anderka MT, Lin AE, Abuelo DN et al: Reviewing the evidence for mycophenolate mofetil as a new teratogen: Case report and review of the literature. Am J Med Genet A, 2009; 149A: 1241–48
11. Armenti VT, Radomski JS, Moritz MJ et al: Report from the National Transplantation Pregnancy Registry (NTPR): Outcomes of pregnancy after transplantation. Clin Transpl, 2003; 131–41

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

12. Roche Laboratories. Important changes in the CellCept [mycophenolate mofetil] prescribing information. In: Use of CellCept is associated with increased pregnancy loss and congenital malformations/change from pregnancy category C to pregnancy category D 2007. Available at: *http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050722s021,050723s019,050758s019,050759s024lbl.pdf*
13. Lin AE, Singh KE, Strauss A et al: An additional patient with mycophenolate mofetil embryopathy: cardiac and facial analyses. Am J Med Genet A, 2011; 155: 748–56
14. Hoeltzenbein M, Elefant E, Vial T et al: Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. Am J Med Genet A, 2012; 158: 588–96
15. Källén B, Westgren M, Aberg A, Olausson PO: Pregnancy outcome after maternal organ transplantation in Sweden. BJOG, 2005; 112: 904–9
16. Schoner K, Steinhard J, Figiel J, Rehder H: Severe facial clefts in acrofacial dysostosis: A consequence of prenatal exposure to mycophenolate mofetil? Obstet Gynecol, 2008; 111: 483–86
17. Parisi MA, Zayed H, Slavotinek AM, Rutledg JC: 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 A, 2009; 149: 1237–40
18. Martín MC, Cristiano E, Villanueva M et al: Esophageal atresia and prenatal exposure to mycophenolate. Reprod Toxicol, 2014; 50: 117–21

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]