

Extensive myocardial infarction in a fetus with cystic fibrosis and meconium peritonitis

Vito Terlizzi*, Andrea Sciarrone[°], Andrew C. Cook[~], Gianni Botta^{°°} and Enrico Chiappa*

*Cystic Fibrosis Centre, AOU Meyer, Florence, Italy

[°]Prenatal Diagnosis Centre, AOU Città della Salute e della Scienza, Turin, Italy

[~]UCL Institute of Cardiovascular Science, University College London, UK

^{°°}Fetal and Maternal Pathology, AOU Città della Salute e della Scienza, Turin, Italy

*Pediatric Cardiology, AOU Meyer, Florence, Italy

Corresponding Author:

Vito Terlizzi, MD

Cystic Fibrosis Centre

AOU Meyer, Florence, Italy

Viale Gaetano Pieraccini, 24

50141, Firenze, Italia

e-mail: terlizzivito@libero.it

telephone: 0039 0555662474

fax: 0039 0555662474

Short title: myocardial infarction in cystic fibrosis

Keywords: cystic fibrosis, meconium peritonitis, myocardial infarction, fetus, carrier screening, cardiac thrombus

Manuscript category: clinical letter

Case Report

An apparently healthy 33 year old primigravida was referred at 32 weeks' gestation to our prenatal diagnosis centre because of progressive distension of the fetal bowel. Within a few days, spontaneous bowel rupture and ascites were documented (Fig. 1). The fetal heart, which had a normal appearance at the routine anomaly scan at 20 weeks, developed severe dysfunction of the left ventricle and contained a hyperechogenic mass. Fetal echocardiogram showed dilation of the heart chambers and severe systolic dysfunction of the left ventricle. A myocardial infarction was suspected and the hyperechogenic mass was interpreted as an intraventricular thrombus (Fig. 2). Genetic analysis for cystic fibrosis (CF) (detection rate 94%) in the asymptomatic parents revealed a heterozygous status for F508del mutation in the father and for N1303K mutation in the mother. Because of rapid deterioration of the fetus a cesarean section was performed. Despite maximal drug therapy and ventilatory support, the baby died a few hours after birth of cardiogenic shock. Autopsy confirmed ileus rupture and diffuse meconium peritonitis. Heart examination confirmed a large thrombus filling most of the cavity of the left ventricle and large area of myocardial infarction involving the interventricular septum, the anterior and lateral wall of the left ventricle (Fig. 3). Investigation of the coronary system revealed endo-luminal thrombosis of the main left coronary artery extending into the proximal left anterior descending and circumflex coronary artery (Fig. 4).

Discussion

Although 80% of cases of meconium ileus (MI) are associated with CF, only 10-20% of CF patients experience this condition [1]. MI usually develops in utero, and may present in the neonate with complete intestinal obstruction requiring either medical or surgical intervention. The success rate of patients with uncomplicated MI, treated with Gastrografin enemas, ranges from 36 to 83% [2]. Immediate surgical intervention is required if there is evidence of intrauterine complication such as perforation, volvulus, or ileal atresia, or if the enema fails to relieve the obstruction after birth [2]. Advances in surgical techniques, total parenteral nutrition, vitamins and elemental diet, and

perioperative care have contributed to the general improvement in the short-term survival of these patients [3]. Efrati et al recently reported that children and adults with CF and a history of MI as neonates show similar nutritional and respiratory status and survival rates as CF control patients without MI [3]. Furthermore, the early diagnosis of newborns with MI may be of benefit, with lower morbidity and increased survival [3]. Nevertheless a lethal course of MI in preterm infants has been described [4].

Sonographic characteristics of MI are neither sensitive nor specific and have been associated with Trisomy 21, intrauterine growth retardation, prematurity, in utero cytomegalovirus infection, intestinal atresia, placental abruption, and fetal demise. Furthermore hyperechogenic bowel has been found to be a normal variant in both the second and third trimesters, [2,5].

To our knowledge, this is the first case of a fetus with CF and MI complicated by myocardial infarction and secondary thrombosis of the left ventricle. The rapid deterioration and sudden onset of such severe complications in our case prevented the opportunity to establish optimal treatment.

A thrombophilic tendency has been described in the CF population but there is limited literature on precise correlation. We speculate that systemic inflammation consequent to chemical peritonitis, in combination with the activation of coagulative factors, was probably responsible for coronary thrombosis, myocardial infarction and severe dysfunction of the left ventricle with secondary ventricular thrombosis in our case. This hypothesis is consistent with the study of Munck et al. [6].

The American College of Obstetrics and Gynecology and the American College of Medical Genetics [7,8] recommend all women of reproductive age should be offered preconception and prenatal CF carrier screening as a routine part of obstetric care, regardless of ethnicity. Nevertheless, its use is still debated. Widespread application has been limited by various ethical questions [9] and since not all CFTR mutations are associated with CF, the results and the detection rate of genetic analysis must be evaluated by a CF-experienced genetic counselor.

In our case, if the pregnant mother had undergone prenatal CF screening, her mutation could have been identified and would have prompted genetic analysis of the couple, possibly predicting the

disease of the fetus and its complications. A higher frequency of MI is expected in patients who are homozygous for class I–II mutations, such as F508del and N1303K [10].

Our case shows that where sonographic signs of MI are suspected in the fetus, a close follow up is necessary as these signs can be associated with severe cardiovascular complications.

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1) Gorter RR, Karimi A, Sleeboom C, Kneepkens CM, Heij HA. Clinical and genetic characteristics of meconium ileus in newborns with and without cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2010; 50:569-72.

- 2) Carlyle BE, Borowitz DS, Glick PL. A review of pathophysiology and management of fetuses and neonates with meconium ileus for the pediatric surgeon. *J Pediatr Surg* 2012; 47:772-81.
- 3) Efrati O, Nir J, Fraser D, et al. Meconium ileus in patients with cystic fibrosis is not a risk factor for clinical deterioration and survival: the Israeli Multicenter Study. *J Pediatr Gastroenterol Nutr* 2010; 50:173-8.
- 4) Puzik A, Morris-Rosendahl DJ, Rückauer KD, et al. Lethal course of meconium ileus in preterm twins revealing a novel cystic fibrosis mutation (p.Cys524Tyr). *BMC Pediatr* 2014; 14:13.
- 5) Scotet V, Duguépéroux I, Audrézet MP, et al. Focus on cystic fibrosis and other disorders evidenced in fetuses with sonographic finding of echogenic bowel: 16-year report from Brittany, France. *Am J Obstet Gynecol* 2010; 203:592.
- 6) Munck A, Kheniche A, Alberti C, et al. Central venous thrombosis and thrombophilia in cystic fibrosis: A prospective study. *J Cyst Fibros* 2015; 14:97-103.
- 7) Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med* 2004; 6: 387–391.
- 8) American College of Obstetricians and Gynecologists Committee on Genetics ACOG Committee Opinion No. 486: update on carrier screening for cystic fibrosis. *Obstet Gynecol* 2011; 117: 1028–1031.
- 9) Castellani C, Massie J. Newborn screening and carrier screening for cystic fibrosis: alternative or complementary? *Eur Respir J* 2014; 43:20-3.
- 10) Castellani C, Cuppens H, Macek M Jr, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. *J Cyst Fibros* 2008; 7:179-96.

Fig. 1: Two-dimensional view of the fetal abdomen at 32 weeks' gestational age showing very large ascites.



Fig. 2: Echocardiographic four-chamber view of the fetal heart showing dilatation of the heart chambers and a very large thrombus filling most of the cavity of the left ventricle. In this diastolic

frame, Color Flow Mapping demonstrates only filling of the right ventricle. Filling of the left ventricle is impaired due both to severe dysfunction of its walls and the thrombus contained within.

LA left atrium, LV left ventricle, RA right atrium, RV right ventricle, T thrombus

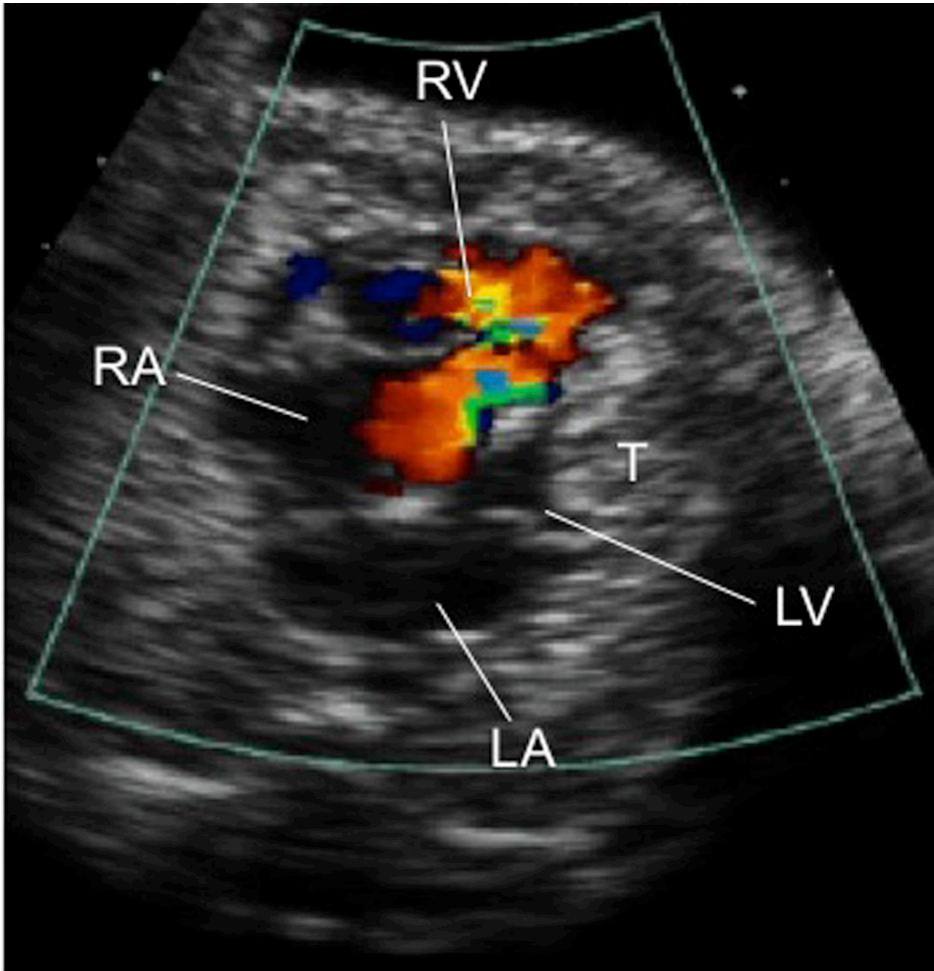


Fig. 3: Specimen of the heart, the left ventricle and the left atrium have been opened along the posterolateral wall. The large thrombus is seen at the apex of the left ventricle extending along the interventricular septum. LA left atrium, LV left ventricle, MV mitral valve, T thrombus.

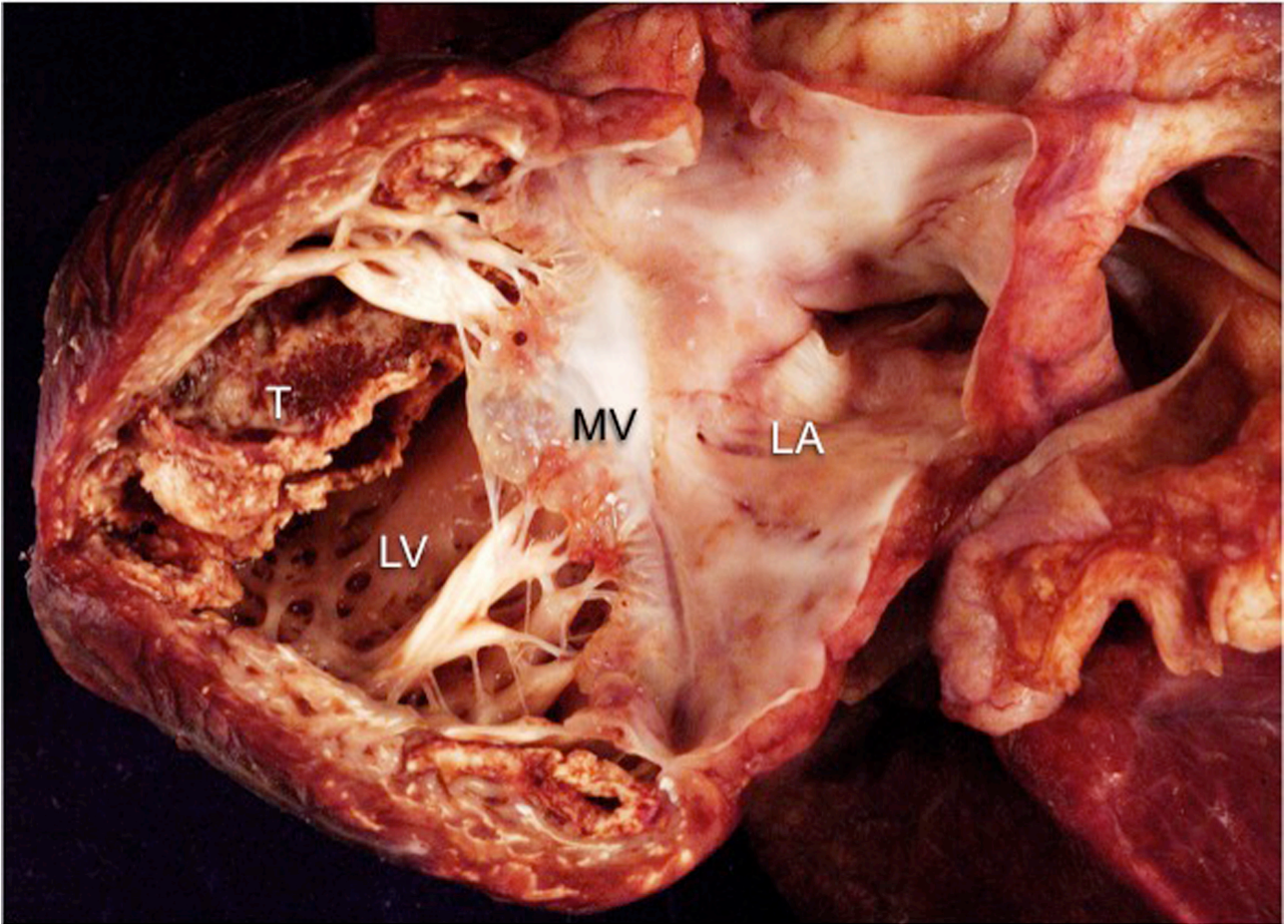


Fig. 4: Short-axis section of the left coronary artery immediately distal to its bifurcation into the anterior descending and circumflex branch. A large thrombus is seen occluding the lumen of both coronaries. CX circumflex coronary artery, LAD left anterior descending coronary artery, T thrombus.

