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Case Report / Olgu Sunumu

Early-onset Marfan syndrome with aortic dilatation and giant pulmonary artery aneurysm: A case report

Aort dilatasyonu ve dev pulmoner arter anevrizmasının eşlik ettiği erken başlangıçlı Marfan sendromu: Olgu sunumu

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ABSTRACT

A 30-year-old woman with ankylosing spondylitis was referred to our clinic with abnormal fetal echocardiography findings, including ascending aortic dilatation, giant main pulmonary artery aneurysm, and aortic and pulmonary valve stenosis at 22 weeks of gestation. The full-term male neonate was born by cesarean section and was transferred to the cardiac intensive care unit soon after delivery for respiratory distress with low percutaneous oxygen saturation. Based on cardiovascular and genetic analysis findings, the patient was diagnosed with Marfan syndrome. Surgery was performed; however, the patient died due to cardiac arrest. In conclusion, main pulmonary artery dilatation and aneurysms are uncommon in Marfan syndrome; therefore, presentation with these findings during the fetal life, as in the present case, is likely a sign of severe Marfan syndrome-related cardiac involvement.

Keywords: Marfan syndrome, prenatal diagnosis, pulmonary artery aneurysm, surgical intervention.

ÖZ

Otuz yaşında ankilozan spondiliti olan kadın gebeliğinin 22. haftasında çıkan aort dilatasyonu, dev ana pulmoner arter anevrizması ve aort ve pulmoner kapak darlığı dahil olmak üzere anormal fetal ekokardiyografi bulguları ile kliniğimize sevk edildi. Sezaryen ile miadında doğan erkek bebek, doğumdan kısa bir süre sonra solunum sıkıntısı ve düşük perkütan oksijen satürasyonu nedeniyle kardiyak yoğun bakım ünitesine yatırıldı. Kardiyovasküler ve genetik analiz bulgularına dayanarak, hastaya Marfan sendromu tanısı kondu. Cerrahi yapıldı, ancak hasta kardiyak arrest nedeniyle kaybedildi. Sonuç olarak, ana pulmoner arter dilatasyonu ve anevrizmaları Marfan sendromunda nadiren görülür; bu nedenle, hastamızda olduğu gibi, fetal yaşam sırasında bu bulguların birlikteliği, Marfan sendromu ile ilişkili ağır kardiyak tutulumun bir belirtisi olabilir.

Anahtar sözcükler: Marfan sendromu, prenatal tanı, pulmoner arter anevrizması, cerrahi girişim.

Marfan syndrome (MFS; OMIM#154700) is an extremely rare genetic connective tissue disorder that predominantly affects the ocular, cardiovascular, and musculoskeletal systems. Cardiovascular complications of MFS are the most common causes of mortality, as they may lead to aortic aneurysm and potential dissection.[1] In this article, we present a case of MFS with ascending aortic dilatation (AAD) and giant pulmonary artery aneurysm (PAA) detected using prenatal echocardiography during the fetal period. To the best of our knowledge, this is the youngest case of early-onset MFS and surgical intervention reported in the literature.

CASE REPORT

A 30-year-old nulliparous woman with ankylosing spondylitis was referred with abnormal fetal echocardiography findings, including AAD, giant main pulmonary artery (MPA) aneurysm, and aortic and pulmonary valve stenosis (AVS and PVS, respectively) at 22 weeks of gestation. Echocardiography was repeated at 28 and 33 weeks of gestation, which showed a large PAA (34.2 and 33.5 mm in diameter, respectively). Gene sequence analysis of the amniotic fluid revealed a gene mutation.

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The full-term male neonate was born by cesarean section, weighing 2.4 kg (3rd percentile), and was 47 cm in length (10th percentile). He was transferred to the cardiac intensive care unit soon after delivery for respiratory distress with low percutaneous oxygen saturation (90%). The clinical features of the patient included plagiocephaly, prominent coronal sutures, posteriorly positioned anterior fontanelle, decreased breath sounds on the left side, and holosystolic heart murmur (Grade 3/4). Based on these abnormal findings, a series of cardiovascular evaluations were performed, which revealed a large aortic and pulmonary root dilatation (PA, 37 mm / Z=12.83; Ao, 25 mm / Z=12.59) (Figure 1, 2a), AVS, mild regurgitation, and a 4.4-mm patent ductus arteriosus (PDA). A computed tomography further revealed total left pulmonary atelectasis due to a left airway compression by the PAA (Figure 2b). The genetic sequence confirmed a missense mutation in the *FBN1* gene (c.2206A>T) of exon 19, resulting in the replacement of asparagine with tyrosine at amino acid residue 736. A genetic study further demonstrated that the mutation was inherited from the mother. According to the 2010 Revised Ghent Nosology for MFS, the patient was diagnosed with MFS based on his cardiovascular and genetic findings.

By two months of age, the patient presented with signs of progressive respiratory distress and congestive

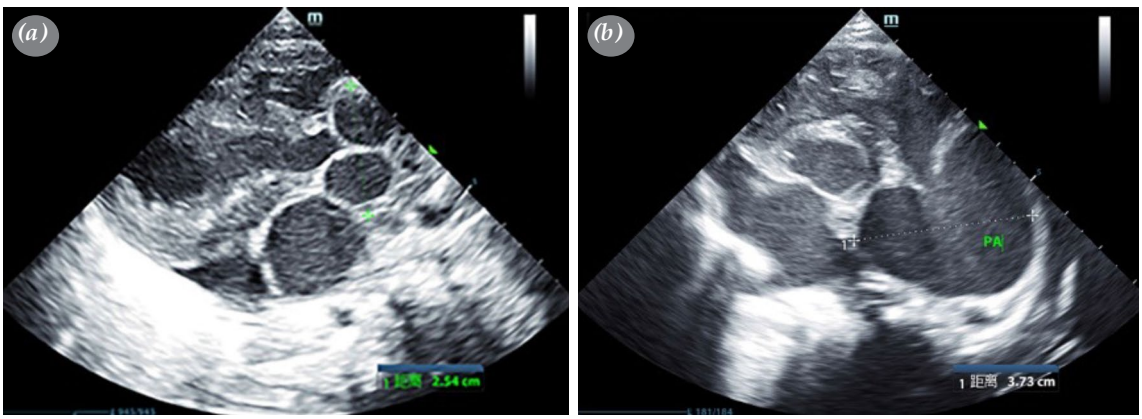

Figure 1. Post-natal echocardiography showing dilatation of **(a)** the aortic artery root and **(b)** the pulmonary artery root.

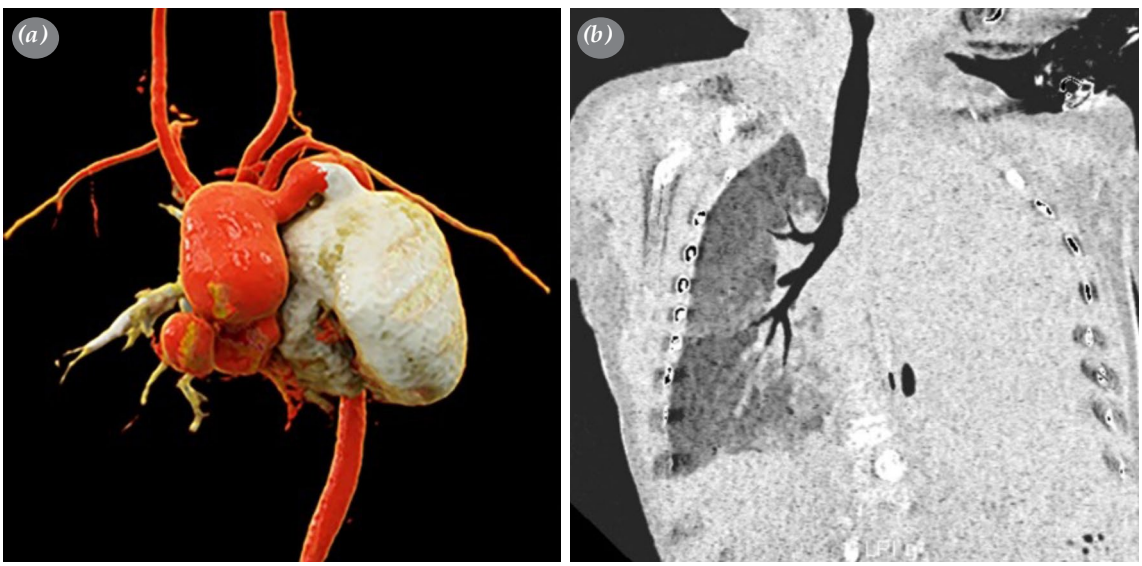

Figure 2. Three-dimensional reconstruction of **(a)** the dilated aortic root and giant pulmonary artery aneurysm and **(b)** the left airway compression sign on chest computed tomography angiography.

heart failure, dyspnea requiring invasive mechanical ventilation support, progressive cardiac dilatation, and persistently high N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (>35,000 pg/mL). Considering poor prognosis of the patient, surgery was decided.

Open heart surgery was performed under cardiopulmonary bypass (total duration: 7.5 h), including ductal ligation, aortic valvuloplasty and ascending aorta reconstruction, pulmonary aneurysmectomy and pulmonary artery reconstruction, and atrial septostomy. Unfortunately, two other serious congenital anomalies, a single coronary anomaly and congenital left pulmonary hypoplasia, were identified during surgery. The patient was administered extracorporeal membrane oxygenation (ECMO) support soon after the surgical procedure, due to severe low cardiac output and massive hemorrhage. After five days of ECMO support, the patient was reluctantly withdrawn from ECMO due to a severe coagulation disorder. The patient experienced cardiac arrest 2 h later, and died despite attempts at emergency resuscitation.

DISCUSSION

Marfan syndrome is an autosomal dominant connective tissue disorder caused by defective microfibrils in association with an *FBN1* mutation on chromosome 15q21.1 and transforming growth factor-beta (TGF-β) overactivity.[1] The most common cause of mortality is cardiovascular complications, such as aortic dilatation and valvular regurgitation. Early-onset MFS is considered the most severe form of MFS and is associated with adverse outcomes and high mortality. Previous reports have indicated that 95% of early-onset MFS patients die within the first year after birth, 85% of whom die from congestive heart failure.[2] This case report is important, as the present case had a unique presentation: cardiac abnormalities identified using fetal echocardiography were exceptionally severe for such an early gestation period, and the severity of the MPA dilatation and the need for such early surgical intervention were also unique.

In general, MFS is rarely diagnosed during the prenatal and neonatal periods due to its various age-dependent clinical manifestations. After searching for articles published in the literature, the majority of MFS-related cardiovascular anomalies detected using fetal echocardiography were in the third trimester, and only one case with a cardiovascular anomaly was initially detected at 22 weeks of gestation,[3] which is similar to our case. The most common MFS-related cardiovascular anomalies were cardiomegaly, aortic root dilatation, valvular regurgitation, and valve prolapse. Pulmonary root dilatation was reported in nine cases, and only one case of them survived at the final follow-up (15 months old).[3,4] The most frequent cardiac manifestation was aortic root dilatation (93%). Among valvular insufficiencies, the most frequent was mitral insufficiency in 81% of patients. In this case, however, no mitral or tricuspid valvular anomaly was detected. According to Stheneur et al.,[5] valvular insufficiency was predictive of shorter life expectancy in MFS patients. This phenotype was considered to be most often secondary to a *de novo* mutation in *FBN1* exons 25 and 26.

A retrospective study of 135 pediatric MFS patients showed that, although 8.1% of patients developed MPA dilatation (Z score ≥2), none required surgical intervention.[5] On the other hand, in the present case, the giant MPA aneurysm volume was so large (42.6×31.6×39.4 mm^3) that it caused severe cardiac and respiratory symptoms, necessitating early surgical intervention. Previous studies have confirmed that aortic root dilatation appears much earlier in those with MPA than in those without MPA.[2] This finding indicates that pediatric MFS patients presenting both aortic and pulmonary root anomalies likely to represent a more severe connective tissue disorder with a poor prognosis, and these symptoms may be a sign of a fatal phenotype and an underlying genotype. Since Hokken et al.[6] proved the similarity in the degenerative media layer of the pulmonary and aortic arteries in patients with MFS, differences in the pressure of the pulmonary and systemic circulation have been thought to play a critical role in determining the time of onset and the degree of dilatation. In our case, we speculated that the left-to-right shunt of the PDA and potential myocardial ischemia for a single coronary anomaly further aggravated perioperative CHF. Congenital left pulmonary hypoplasia exacerbated respiratory distress, except for compression from the PAA.

In conclusion, this case report highlights that main pulmonary artery dilatation and aneurysms are uncommon in Marfan syndrome; therefore, presentation with these findings during the fetal life, as in the present case, is likely a sign of severe Marfan syndrome-related cardiac involvement.

Patient Consent for Publication: A written informed consent was obtained from parents of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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