

What is your diagnosis?

A 21-year-old patient presented during her first pregnancy at 34 weeks gestation. Her medical history was unremarkable, except that her husband was her cousin. During ultrasound evaluation of the fetus nothing remarkable except hyperechogenicity in the base of the heart was observed. This hyperechogenicity was observed both in the ascending aorta and main pulmonary artery (Figure 1a, b). Other fetal echocardiographic findings were normal, including cardiac position, situs, rhythm, size of the chambers, and main arteries. The toxoplasma, rubella, cytomegalovirus, herpes, syphilis (TORCH) panel was negative for recent infection. During her follow-up visit at 37 weeks gestation, new findings like hyperechogenicity in the abdominal aorta, inferior vena cava, and placenta were noted (Figure 2a, b). At 40 weeks gestation, she delivered a 3215 g male fetus with an APGAR score of 9/10 (1st and 5th minute) by C-section because of prolonged labor. His postnatal echocardiographic evaluation showed same findings.

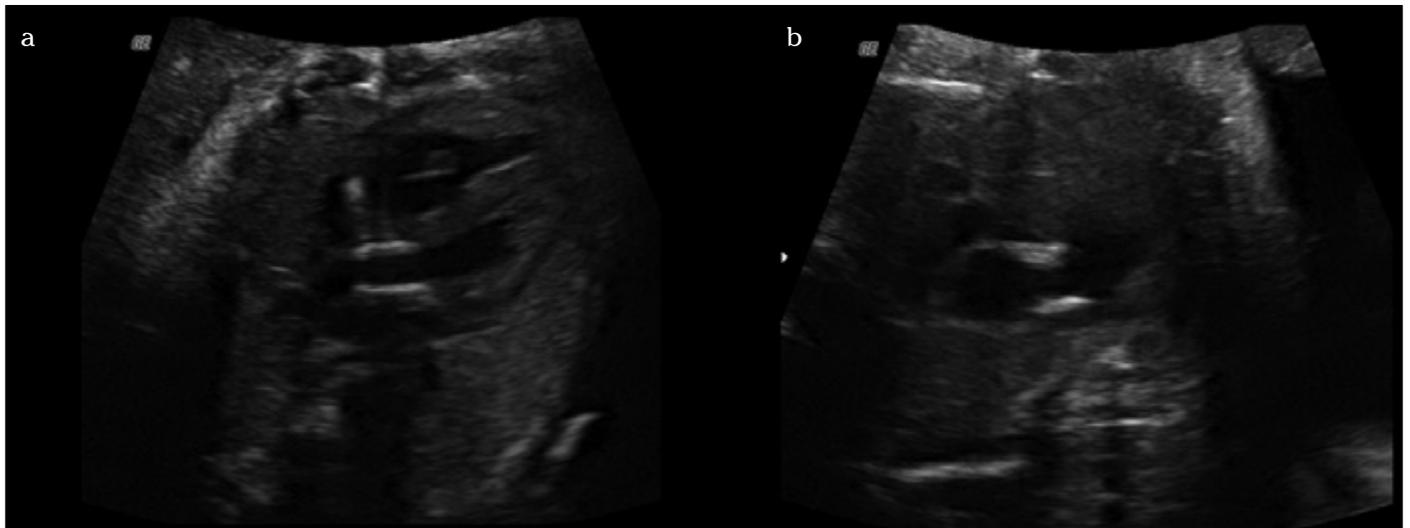


Figure 1. a, b. Hyperechogenicity in the great vessels. Aorta (a) main pulmonary artery (b)

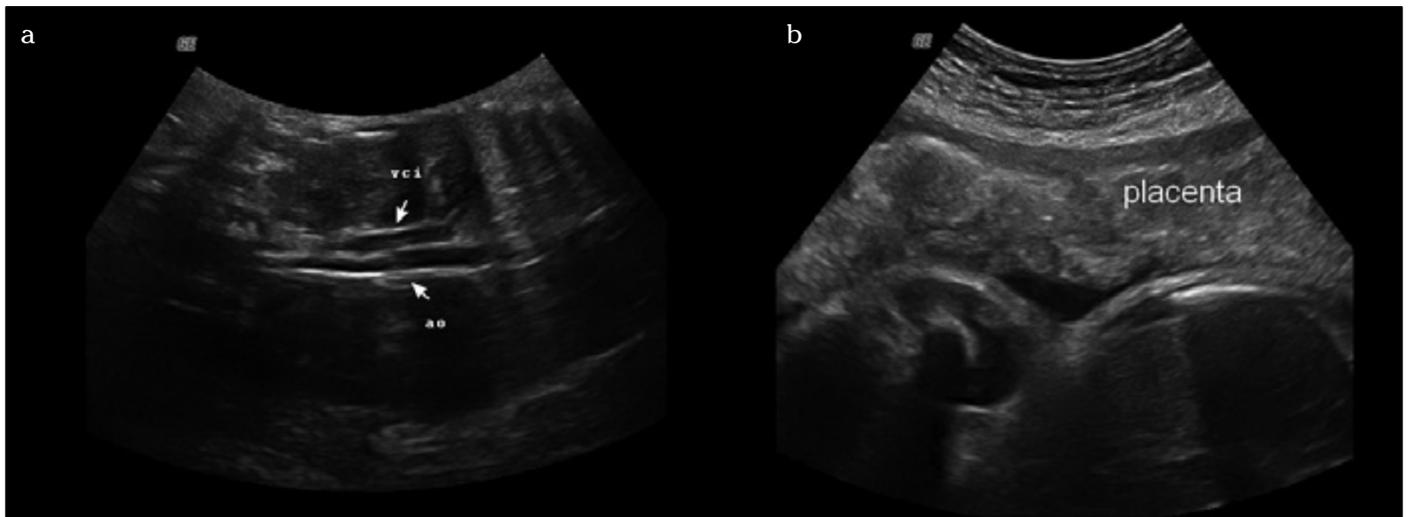


Figure 2. a, b. Hyperechogenicity in the vena cava inferior (vci) and abdominal aorta (ao) (a) hyperechogenic foci in the placenta (b)



Answer

Postnatal echocardiography revealed patent ductus arteriosus as an additional finding. His abdominal ultrasound revealed diffuse vascular calcifications in the abdominal aorta and celiac trunk. Renal parenchymal calcifications were also noted. The patient was diagnosed with idiopathic infantile arterial calcification (IIAC). He was discharged from the hospital on post-natal 13th day. He was administered pamidronate, captopril, and furosemide for hypercalcemia and hypertension. Genetic analysis from peripheral blood of the infant revealed homozygote ectonucleotide pyrophosphate/ phosphodiesterase 1 (ENPP1) gene mutation (p.G738R [c.2212G>A]), which further confirmed the diagnosis. His parents were found to be heterozygote carriers of this mutation.

At the time of this report, the infant was eight months of age; hyperechogenicity in the abdominal aorta and renal parenchyma and patent ductus arteriosus were still persisting. He was still undergoing antihypertensive therapy.

IIAC, also known as generalized arterial calcification of infancy, is a very rare disease that was first reported in 1901 by Bryant and White. (1) Among nearly 200 cases reported until now, few have been prenatally diagnosed. It is inherited in an autosomal recessive pattern. It is characterized by disruption and calcification of the internal elastic lamina of the fetal arteries with calcium deposits, leading to fibrosis and occlusion of the arteries. (2) It is therefore almost always fatal. Fetuses with this disorder either develop cardiac failure and hydrops in utero or are born acutely ill with unstable cardiac functions. Among the survivors beyond the newborn period, few cases were reported to live until adulthood. (3) The gene responsible for this disease was found to be the ENPP1 gene, which is located on the long arm of sixth chromosome. This cell surface enzyme generates inorganic pyrophosphate (PPi), a solute that regulates cell differentiation and serves as an essential physiological inhibitor of calcification (4). Other genes that are also thought to be related to the disease are ATP-binding cassette, sub-family C member 6 (ABCC6), 5'-nucleotidase, ecto (NT5E) and solute carrier family 20, member 2 (SLC20A2). They all play a role in phosphate metabolism. Although bisphosphonates were used postnatally, no successful antenatal therapy with these drugs has been reported until now.

Main antenatal ultrasound findings are hyperechogenicity in great arteries (aorta, pulmonary artery), polyhydramnios, and pericardial effusion. In advanced cases, cardiac failure and hydrops may develop (5).

The diagnosis of IIAC is clinically confirmed by ruling out other disorders associated with systemic calcium deposition, such as hyperparathyroidism, hypervitaminosis D, and metastatic calcification from renal disease (6). Most cases in literature base

their postnatal definitive diagnosis on radiographical examinations, echocardiography, and autopsy. That's because, the demonstration of calcifications with these methods is not difficult. Genetic investigation for the mutation in ENPP1 in antenatally diagnosed cases is undertaken in very few cases together with ours (6-8). Either homozygote or combined heterozygote mutations can cause the disease (6).

Currently, there is no prenatal treatment for this disease. As the rates of prenatal diagnosis of this disease increase, studies regarding in utero treatment will ultimately increase. In order to increase prenatal diagnosis rates, clinicians should be careful regarding the echogenicity of the great vessels during antenatal ultrasound evaluation. Determining the mutation will also provide first degree relatives of the parents to be tested and counseled for this lethal disease.

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