Generalized arterial calcification of infancy – Fetal diagnosis to postnatal management

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ABSTRACT

Generalized arterial calcification of infancy is a rare entity with poor fetal and postnatal outcomes and high morbidity in survivors. Half of the cases are diagnosed intrauterine due to hemodynamic compromise, and the associated manifestations pose unique management challenges. We hereby report an account of a fetal diagnosis in a referral for hydrops with postnatal evaluation and management.

Keywords: Fetal cardiac dysfunction, generalized arterial calcification of infancy, hydrops, idiopathic arterial calcification

INTRODUCTION

Generalized arterial calcification of infancy (GACI) is a rare condition, with only about 250 cases reported in the literature since it was first described in 1899.[1] Nearly half of the cases are diagnosed *in utero*.[2] It is fatal in a large proportion of patients (50%–85%) by 6 months of age, while one-fourth succumb in the fetal period.[3] Survivors may have persistent arterial stenoses leading to cardiovascular and ischemic complications.[2] Ultrasound (US) and computed tomography (CT) are the most common modalities for the initial imaging evaluation and follow-up. Early institution of therapy may promote regression of vascular calcification in patients.[4]

CASE REPORT

A 28-year-old multigravida with four previous spontaneous abortions was referred because of pericardial effusion at 33 weeks + 5 days period of gestation. The previous abortions occurred in the first trimester. Genetic analysis of the abortus in the last pregnancy by karyotype and fluorescence *in situ* hybridization was normal. Fetal echocardiography revealed marked echogenicity circumferentially along the aortic annulus, wall of the ascending aorta, transverse arch, and descending thoracic aorta (DTA). There was severe right ventricular dysfunction with massive pericardial effusion [Figure 1]. The pulmonary annulus, main pulmonary artery (PA), and proximal branch PA were also calcified. Under close monitoring for fetal well-being, pregnancy was continued until term. A 2.5-kg child was delivered vaginally with an uneventful perinatal transition. Echocardiography confirmed the hyperechogenicity in areas corresponding to the fetal evaluation [Figure 2]. CT showed calcification of DTA, iliac arteries, and internal carotid arteries [Figure 3].

Further evaluation aimed at assessing associated lesions secondary to ectopic calcification, including hearing, serum, and urinary calcium levels, and serum phosphate levels were noted to be normal. Pamidronate infusion was administered at 0.5 mg/kg/day for 3 days. The patient had asymptomatic hypocalcemia requiring

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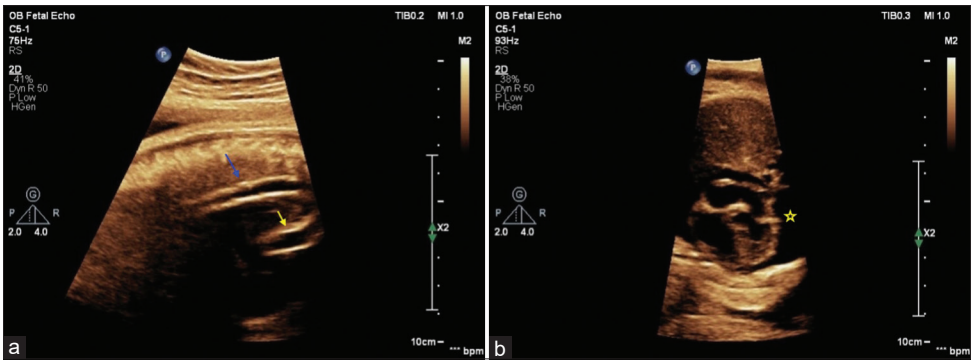

Figure 1: Fetal echocardiography (a) Aortic arch view showing the hyperechoic ascending aorta (yellow arrow), transverse arch, and descending thoracic aorta (blue arrow) (b) Four-chamber view showing large pericardial effusion (*)

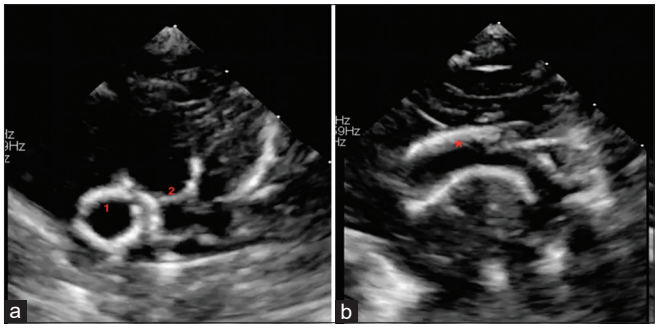

Figure 2: Transthoracic echocardiography (a) A parasternal-short-axis view at the great arterial level showing hyperechoic walls of the aorta and pulmonary artery showing 1: aorta, 2: the pulmonary artery with hyperechoic walls, (b) Suprasternal arch view showing hyperechoic walls of ascending aorta and arch (*)

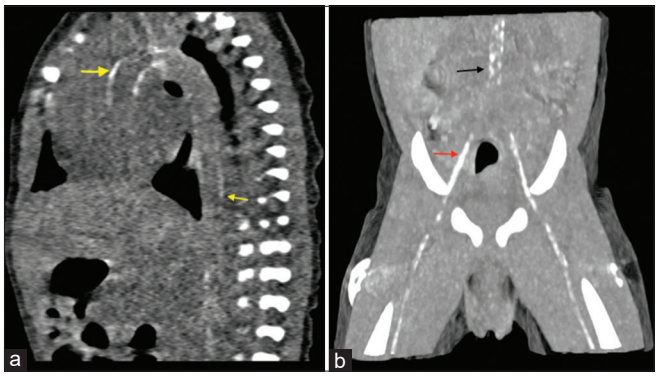

Figure 3: (a) Sagittal long axis computed tomography (CT) showing calcification involving ascending aorta and descending thoracic aorta (arrows) (b) Coronal CT image showing calcification in the abdominal aorta (black arrow), common iliac (red arrow) and its branches bilaterally

supplementation after the 3rd day of infusion. The genetic workup sent was noted to be a homozygous mutation in ABCC6 at exon 5 C.496C>T responsible for GACI (OMIM#614473). Further plan is to monitor with low-dose CT for progression/regression of vascular calcification, urinary calcium levels and ventricular function at follow up. A repeat course of bisphosphonates shall be considered accordingly.

DISCUSSION

GACI, an autosomal recessive disorder affecting 1:200,000 people, is characterized by severe calcifications of the media of large and medium-sized arteries, accompanied by intimal proliferation leading to arterial stenosis. It was first described in 1899; approximately 250 cases have been reported worldwide.[1,4] Around 75% of GACI cases are due to ENPP1 mutations, while 9%–10% are attributed to a mutation in ABCC6, which helps transport nucleotide triphosphates into extracellular space. Its exact role in GACI is not understood yet.[5] There are genotypic and phenotypic similarities between pseudoxanthoma elasticum and autosomal recessive hypophosphatemic rickets-2.[6] As in our case, nearly half of cases are diagnosed in fetal life.[7] Intrauterine presentation usually involves hydrops, polyhydramnios, and fetal compromise. Late-onset variants present with respiratory distress, feeding difficulty, cyanosis, and other signs of cardiovascular compromise within 3 months of postnatal life.[2] Early-onset disease commonly involves hepatic, aortic, and pulmonary arteries, while late-onset disease is known to involve coronaries and renal arteries.[2] The peripheral arterial calcification may present as diminished pulses, ischemic ulcerations, or gangrene.

Extravascular manifestations involve calcifications in the myocardium, liver, kidneys, and periarticular calcifications.[1] Hearing loss (sensory neural or conductive or mixed) has been described with ENPP1 mutation and is multifactorial.[8] Dental abnormalities such as infraocclusion, ankylosis, and retained primary teeth are described.[9] Currently, our case lacks any extravascular, internal organ calcification, or hearing impairment. GACI patients who survive infancy may develop hypophosphatemic rickets.[10]

In the absence of an established regimen, many agents currently employed are supportive, with little evidence of a definitive cure. Bisphosphonates have been used in GACI since 1970. The GACI therapeutic goal is to

inhibit bone mineralization instead of bone resorption. Etidronate, a first-generation bisphosphonate acting predominantly on bone mineralization, is frequently used in GACI.[6] In our case, we used pamidronate as etidronate was not available. The current regimen used draws similarities from that employed for osteogenesis imperfecta. Sodium thiosulfate, which increases the solubility of calcium, has been used to treat ectopic calcifications caused by renal failure, dermatomyositis, and hyperphosphatemic tumoral calcinosis with its calcium chelating property.[6] Other supportive measures involve standard therapy for hypertension, Vitamin D and phosphorous in hypophosphatemic rickets, aspirin for coronary stenosis, anti-VEGF (vascular endothelial growth factors) in retinoid streaks, and hearing aids if there is hearing loss.

Monitoring for vascular calcification forms an essential aspect of follow-up and management. The current practice for follow-up includes CT imaging every 3–4 months during infancy and after that 6 monthly in the 2nd year of life or potentially discontinued if calcifications resolve.[5] Echocardiography to monitor the degree of myocardial dysfunction and hearing evaluation and ophthalmic screening should begin in early childhood. Developmental monitoring is considered in all infants who survive this critical period.[4]

Future directions in managing GACI include enzyme replacement therapy to replace deficiency caused by ENPP1 mutation. A study (phase 1b) in the US assessing the safety of the use of ENPP1 enzyme replacement therapy in infants (genetically proven, >1 month) is ongoing and has shown success in mouse models.[6]

CONCLUSIONS

GACI is a fatal disease with high mortality in the neonatal or infantile age. Mortality in GACI is due to cardiovascular compromise, including myocardial ischemia/infarction, heart failure, persistent pulmonary hypertension, and multiorgan failure. Bisphosphonates remain the mainstay of treatment until gene therapy becomes established.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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