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Varied Imaging Manifestations in EFEMP2 Related Cutis Laxa Associated Arterial Tortuosity

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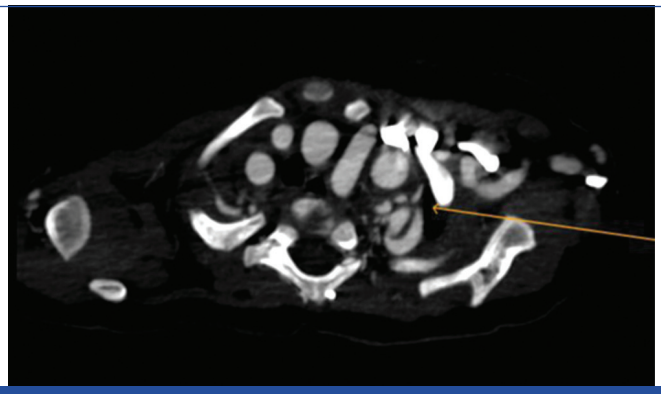
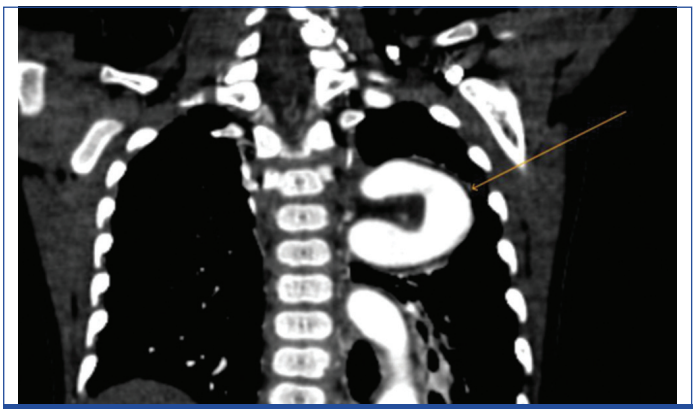
Keywords: Autosomal recessive cutis laxa type 1B, Epidermal growth factor containing fibulin extracellular matrix protein 2, Multisystem disease, Vascular structures

CASE 1

An eight-month-old male baby was brought to the hospital by his parents due to poor weight gain, lower respiratory tract infection, and exertional dyspnoea (noticed by the parents) for one month. During the clinical examination, a grade-III ejection systolic murmur and end diastolic murmur were observed. A hyperdynamic apex and mild tachypnoea were also noted. Echocardiography (ECHO) was performed to investigate the suspicion of cardiac disease. The ECHO revealed aneurysmal aortic dilatation, moderate to severe aortic regurgitation, and was suggestive of Arterial Tortuosity Syndrome (ATS). Subsequently, a Computed Tomography (CT) pulmonary angiogram was conducted [Table/Fig-1-8].



[Table/Fig-1]: a) Axial CT reconstruction of CT pulmonary angiogram with aortogram reveals a cluster of vessels sign in the superior mediastinum (orange arrow).

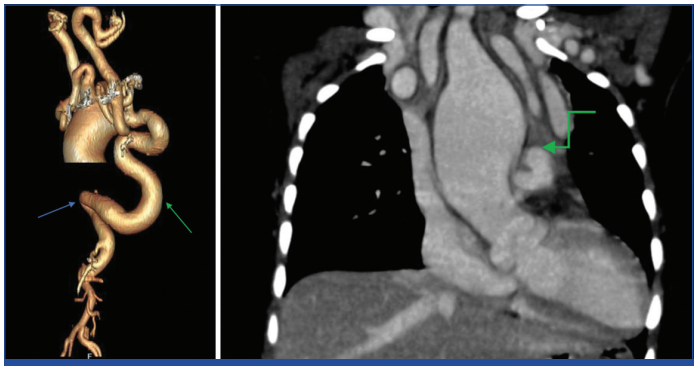


[Table/Fig-2]: Coronal CT shows lateral location of tortous aorta (orange arrow) reaching to mid thoracic cavity: meandering vessel sign.

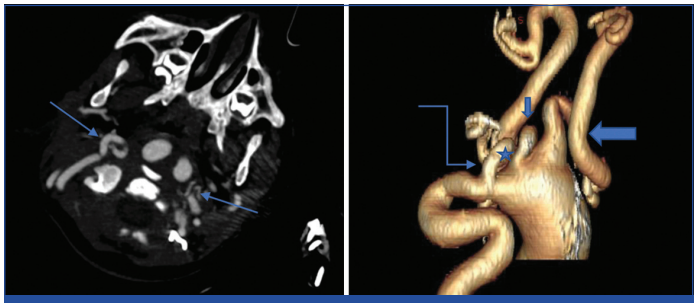
At the time of discharge, the baby was stable and able to tolerate feeds. The caregivers were counselled regarding the progressive nature of the disease, its genetic aetiology and the prognosis.

CASE 2

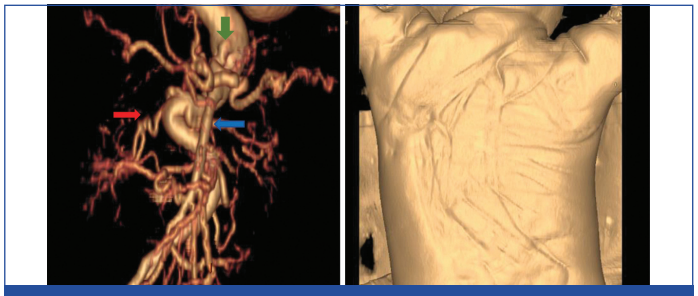
A 10-month-old female baby, who was developmentally normal, presented with complaints of breathing difficulty that worsened in the lying down position and improved in the sitting position, as well as decreased urine output for the past two weeks. There was no significant antenatal, natal or postnatal history. The baby had a history of head sweating and a suck-rest-suck cycle. There was no history of cough.



[Table/Fig-3]: A Three Dimensional (3D) volume rendered image shows global sign of gross aortic dilatation and tortuosity (green arrow) with kinking of the vessel (blue arrow): Aortic elongation sign.
[Table/Fig-4]: Coronal CT shows early bifurcation of pulmonary artery with "V" configuration: V sign of pulmonary bifurcation (curved arrow). (Images from left to right)

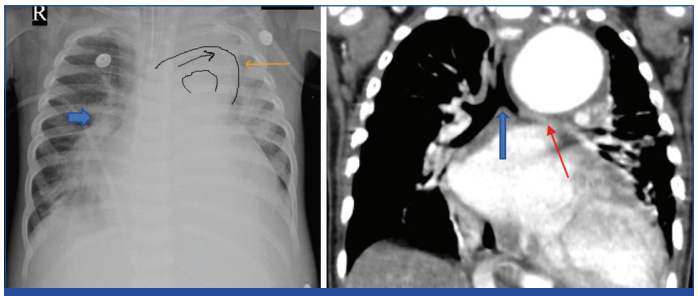


[Table/Fig-5]: Axial CT shows extreme tortuosity and meandering course of bilateral internal carotid arteries (blue arrows).
[Table/Fig-6]: Volume Rendering (VR) image (posterior view) shows dilated and tortous Innominate artery (thick blue arrow), left common carotid artery (thin blue arrow) and left subclavian artery (curved arrow). Significant luminal narrowing at areas of kinks (asterisk). (Images from left to right)

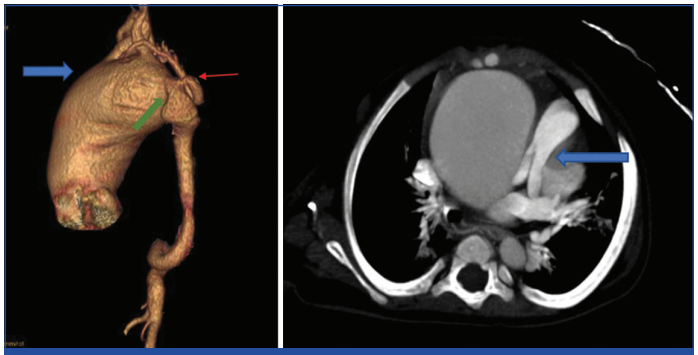


[Table/Fig-7]: A 3D rendered image of abdominal aorta and visceral arteries shows tortuosity in the coeliac (green arrow), superior (blue arrow) and inferior mesenteric artery. Also, in renal arteries (red arrow).
[Table/Fig-8]: Surface rendered 3D reconstruction of the same patient illustrates excessive skin laxity leading to multiple redundant skin folds. (Images from left to right)

Upon clinical examination, cutis laxa was observed along with a hyperdynamic apex, cardiomegaly, an ejection systolic murmur, an end diastolic murmur, tachypnoea and subcostal retractions. ECHO showed dilated aorta from the sinuses to the proximal arch, aneurysmal dilation of the ascending aorta, tortuous descending aorta, severe mitral regurgitation, aortic regurgitation and pulmonary artery hypertension. Multidetector Computed Tomography (MDCT) pulmonary angiogram was advised to further assess the anatomy of the vessels [Table/Fig-9-12].



[Table/Fig-9]: Frontal chest radiograph shows elongated tortous aorta-aortic elongation sign (yellow arrow) and dilated descending pulmonary artery (black arrow).
[Table/Fig-10]: Coronal reconstruction of Contrast-enhanced Computed Tomography (CECT) image shows splaying of carinal angle (blue arrow) due to cardiomegaly and mild indentation of left pulmonary artery by the tortuous vessels (red arrow). (Images from left to right)

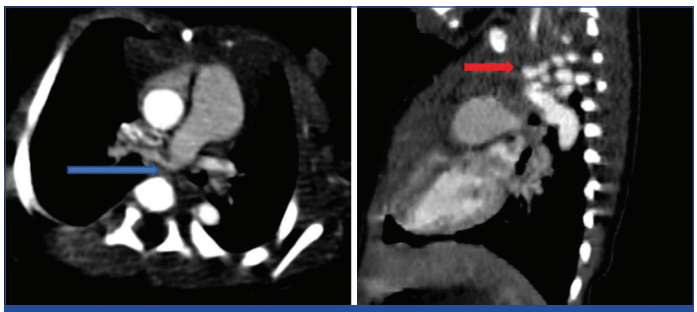


[Table/Fig-11]: A 3D volume rendering image (oblique view) shows marked dilatation and tortuosity of proximal arch upto the level of ductus towards right side (blue thick arrow) and kinking and narrowing at the level of ductus (green arrow) and at origin of left subclavian artery (red arrow).
[Table/Fig-12]: Axial CECT image-"INVERTED V" shape configuration of pulmonary artery bifurcation (blue arrow) and relative narrowing of proximal parts of right and left pulmonary artery. (Images from left to right)

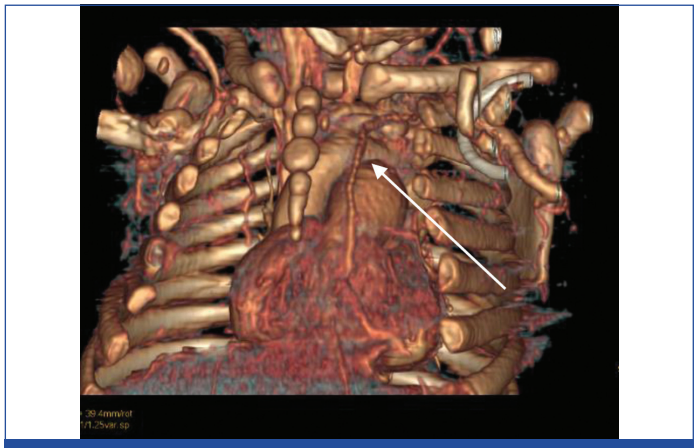
Initially, the baby was stable and able to tolerate feeds. However, four months after the diagnosis, the patient developed severe respiratory distress. Venous blood gas analysis showed severe respiratory acidosis. The baby was intubated and started on inotropes and diuretics. While being extubated, the patient was unable to tolerate Bilevel Positive Airway Pressure (BiPAP) and experienced bradycardia, desaturation, and ultimately succumbed to death despite resuscitative measures.

CASE 3

A male baby, born at term and appropriate for gestational age, was referred from an outside hospital at 78 hours of life (HOL) due to respiratory distress. Clinical examination at 48 HOL revealed a systolic murmur. Chest X-ray showed well-expanded lung fields and normal cardiac shadows. Sepsis screen and blood culture were negative. ECHO was performed, which revealed a dilated main pulmonary artery and ascending aorta, myxomatous Arteriovenous (AV) valve leaflets, severe bilateral peripheral Pulmonary Stenosis (PS), turbulent flows across the arch vessels and descending aorta, Right Pulmonary Artery (RPA) stenosis, and moderate Pulmonary Arterial Hypertension (PAH). Due to suspicion of ATS, a CT pulmonary angiogram was conducted. The CT pulmonary angiogram showed levocardia, mild tortuosity and elongation of the aortic arch, tortuosity of the origin and course of bilateral common carotid and left subclavian arteries, tortuous aberrant right subclavian artery, dilated main pulmonary artery (12.8 mm) with narrowing of the origin of the left pulmonary artery (3.4 mm), and mild tortuosity of the descending thoracic aorta and inferior mesenteric artery was [Table/Fig-13-15]. The baby remained haemodynamically stable and had good oral feeding tolerance, leading to his discharge.

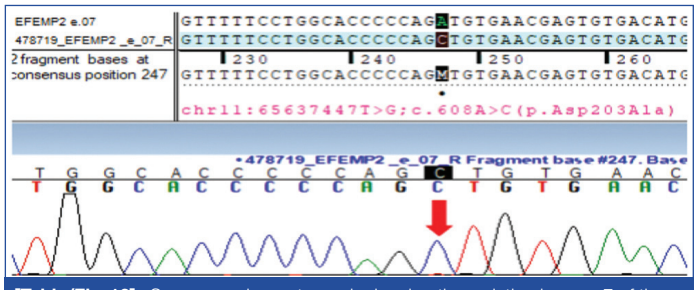


[Table/Fig-13]: Dilated main and right pulmonary artery with tortuous stenosed RPA branches (blue arrow).
[Table/Fig-14]: Sagittal CT reconstruction of CECT reveals multiple rounded vascular structures in the superior mediastinum cluster of vessels sign (red arrow). (Images from left to right)



[Table/Fig-15]: A 3D VR images: In addition to dilated main pulmonary artery and ascending aorta, hypertrophied left internal mammary artery can be seen (white arrow).

Genetic testing revealed that all of these babies had a similar genetic result, with a mutation in the Epidermal Growth Factor-containing Fibulin-like Extracellular Matrix Protein 2 (EFEMP2) gene causing Autosomal Recessive Cutis Laxa type 1B (ARCL1B) associated with arterial tortuosity. Specifically, a homozygous missense variation in exon 7 of the EFEMP2 gene (chr11:65637447T>G; c.608A>C) resulting in the substitution of alanine for aspartic acid at codon 203 (p.Asp203Ala) was identified, confirming the diagnosis of ARCL1B [Table/Fig-16].



[Table/Fig-16]: Sequence chromatograph showing the variation in exon 7 of the EFEMP2 gene.

DISCUSSION

The gene EFEMP2 related cutis laxa, also known as autosomal recessive cutis laxa type 1B (ARCL1B), is a rare multisystem disease that affects the skin, skeleton and vascular structures [1]. ARCL1B is caused by mutations in the EFEMP2 gene located on chromosome 11q13.1, which encodes the EFEMP2. The severity of the disease can range from perinatal death to a spectrum of disease compatible with survival [2].

This condition is characterised by cutis laxa, facial dysmorphism, arterial involvement (arterial tortuosity, aneurysms, or stenosis), respiratory involvement (emphysema, diaphragmatic hernia, or hypoplasia), craniofacial involvement (retrognathia, widely spaced eyes, and high palate), bony deformities (scoliosis and chest wall abnormalities), and other features commonly seen in connective tissue disorders, such as joint laxity and arachnodactyly. The affected arteries are typically large and medium-sized vessels [3].

Loeys-Dietz syndrome, Occipital horn syndrome, connective tissue diseases including Ehler-Danlos syndrome-type III and Ehler-Danlos syndrome-vascular type IV, wrinkly skin syndrome, Gerodermia osteodysplastica, Marfan syndrome, and Menkes disease can present with typical features that mimic ARCL1B [4]. Genetic testing is the gold standard for diagnosing these mimics. Fibrillin-1 (FBN1) mutations can help differentiate between these conditions. For example, an FBN1 mutation is specific for Marfan syndrome, Transforming Growth Factor Beta Receptor 1 (TGFBR1) or TGFBR2 mutations are associated with Loeys-Dietz syndrome (LDS), and Collagen alpha-1(III) (COL3A1) and Collagen type I alpha 1 (COL1A1) mutations are seen in vascular Ehlers-Danlos syndrome (EDS). The ATPase Copper Transporting Alpha (ATP7A) gene is responsible for occipital horn disease, and biallelic pathogenic variants in the SLC2A10 gene are associated with ATS.

The Tortuosity Index (TI) of intracranial arteries can also aid in distinguishing between Marfan syndrome and LDS. An intracranial ICA TI greater than 132 shows higher specificity (98%) for connective tissue disorders, like Marfan syndrome, while a Vertebral basilar system TI greater than 60 is 97% specific for LDS [4]. Awareness of the early signs of arterial tortuosity in ARCL1B and recognition of the described signs (such as the aortic elongation sign and "V" sign of the pulmonary artery) can lead to early diagnosis of clinically asymptomatic cases.

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