International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Case Report

Diffuse Vascular Calcification Presenting as Refractory Pulmonary Hypertension in a Neonate: A Diagnostic Unravelling

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Received: 02-02-2026
Accepted: 20-02-2026
Available online: 03-05-2026

ABSTRACT

Background: Persistent pulmonary hypertension of the newborn (PPHN) is a recognized cause of neonatal hypoxemic respiratory failure, most commonly associated with parenchymal lung disease or maladaptation of pulmonary circulation. Rarely, severe and refractory pulmonary hypertension may signal an underlying systemic vasculopathy. Generalized arterial calcification of infancy (GACI) is a rare genetic disorder characterized by diffuse arterial wall calcification and intimal proliferation, frequently resulting from ENPP1 mutations. Early manifestations may mimic common neonatal cardiopulmonary conditions, leading to diagnostic delay.

Case Presentation: We report a late preterm neonate (34+5 weeks) presenting at birth with severe respiratory failure and persistent hypoxemia requiring mechanical ventilation. Initial evaluation suggested respiratory distress syndrome with severe pulmonary hypertension. Despite optimized ventilatory support, surfactant therapy, pulmonary vasodilators, and inotropic support, pulmonary hypertension remained refractory. The emergence of systemic hypertension, depressed biventricular function, and differential oxygen saturations prompted further evaluation. Serial imaging revealed progressive arterial wall echogenicity on echocardiography and abdominal ultrasonography. Plain chest radiography demonstrated linear, tubular radio-opaque densities tracking along major vascular pathways, mimicking intravascular lines. Contrast-enhanced CT angiography confirmed extensive circumferential calcification involving the thoracic and abdominal aorta, pulmonary arteries, and major systemic branches with preserved luminal patency. Genetic testing identified a pathogenic ENPP1 mutation, establishing the diagnosis of generalized arterial calcification of infancy. The patient was managed with intensive cardiopulmonary support, antihypertensive therapy, and bisphosphonate treatment.

Conclusion: This case highlights generalized arterial calcification of infancy as an important differential diagnosis in neonates with refractory pulmonary hypertension, particularly when accompanied by early systemic hypertension and atypical vascular imaging findings. Careful review of plain radiographs and progressive arterial wall echogenicity on ultrasound may provide early diagnostic clues. Prompt recognition and genetic confirmation are essential for targeted management, prognostication, and family counseling in this rare but potentially fatal neonatal vasculopathy.

Keywords*: Generalized arterial calcification of infancy; ENPP1 deficiency; Persistent pulmonary hypertension of the newborn; Neonatal systemic hypertension; Vascular calcification; Neonatal vasculopathy.*

BACKGROUND

Persistent pulmonary hypertension of the newborn represents a well-recognized cause of early neonatal hypoxemic respiratory failure and is most commonly encountered in association with parenchymal lung disease, perinatal asphyxia, infection, or maladaptation of the transitional pulmonary circulation. In the majority of affected neonates, pulmonary hypertension demonstrates a predictable response to established supportive strategies, including optimized ventilation, surfactant replacement when indicated, and targeted pulmonary vasodilation.[1] However, a subset of neonates exhibit pulmonary hypertension that is disproportionately severe, refractory to conventional therapy, or accompanied by systemic cardiovascular findings that are not readily explained by primary pulmonary pathology alone.[2] (In such contexts, persistence of extreme pulmonary pressures, early ventricular dysfunction, or the coexistence of systemic hypertension may signal an alternative or occult disease process, necessitating re-evaluation of initial diagnostic assumptions.[3]

Rare neonatal vasculopathies constitute an important but frequently under-recognized group within this differential, particularly when early manifestations are nonspecific and overlap with common neonatal cardiopulmonary conditions. Disorders characterized by diffuse arterial involvement may initially present with respiratory failure, myocardial compromise, or circulatory instability before structural vascular abnormalities become clinically or radiologically apparent.[4] Advances in echocardiography and cross-sectional imaging have increasingly highlighted the role of arterial wall pathology in such presentations, revealing patterns of vascular involvement that extend beyond the pulmonary circulation and challenge traditional diagnostic frameworks. Recognition of these entities is critical, as delayed diagnosis may obscure the unifying etiology underlying multisystem involvement and limit opportunities for targeted intervention.[5,6]

CASE PRESENTATION

Perinatal History and Early Clinical Course (Day 0–Day 2)

A late preterm female neonate was delivered at 34 weeks and 5 days of gestation to a 32-year-old mother by emergency lower-segment caesarean section for reduced fetal movements. The antenatal course was notable for gestational diabetes mellitus diagnosed during the third trimester and polyhydramnios detected on ultrasonography. A single dose of antenatal corticosteroid had been administered approximately six hours prior to delivery. No structural anomalies were identified on routine antenatal imaging, and fetal echocardiography with Doppler assessment was reported as normal. The sequence of clinical events and key diagnostic milestones is summarized in Table 1.

At birth, the neonate exhibited poor respiratory effort with generalized cyanosis and required immediate endotracheal intubation in the operating theatre. Following initial stabilization, the infant was transferred to the neonatal intensive care unit and commenced on invasive mechanical ventilation. Early postnatal adaptation was marked by persistent hypoxemia despite ventilatory support, with preductal oxygen saturation remaining low and requiring a fraction of inspired oxygen of 1.0 to maintain acceptable systemic oxygenation. Initial arterial blood gas analysis demonstrated mild respiratory acidosis without severe metabolic derangement.

A chest radiograph obtained shortly after admission revealed features consistent with respiratory distress syndrome, including reduced lung volumes and prominent air bronchograms. In view of prematurity and radiographic findings, exogenous surfactant was administered at a standard therapeutic dose. Despite surfactant replacement and optimized ventilatory settings, oxygenation improved only marginally, and significant oxygen dependency persisted during the first 24 hours of life. The chest radiograph also demonstrated multiple linear, tubular radio-opacities tracking along the expected anatomical course of major vessels, creating an ***appearance of reminiscent of multiple intravascular lines*** despite absence of such devices (Figure 1).

Targeted cardiovascular evaluation was undertaken because of ongoing hypoxemia disproportionate to the degree of parenchymal lung disease. Transthoracic echocardiography demonstrated elevated pulmonary arterial pressures with evidence of a small patent ductus arteriosus showing bidirectional shunting. Both right and left ventricular systolic functions were depressed, and the right ventricle appeared dilated. These findings were interpreted as consistent with severe persistent pulmonary hypertension of the newborn, and medical management was initiated accordingly.

During the second day of life, the clinical course remained dominated by refractory hypoxemia and cardiovascular instability. Differential oxygen saturation between upper and lower extremities was observed, with persistently lower postductal values. Inotropic support was escalated in response to ventricular dysfunction, and pulmonary vasodilator therapy was introduced. Despite these measures, pulmonary pressures remained markedly elevated on repeat echocardiographic assessment, and myocardial performance showed limited early recovery. No overt signs of sepsis, metabolic disturbance, or structural cardiac obstruction were evident at this stage, and the clinical picture continued to be managed within the working diagnosis of severe pulmonary hypertension complicating prematurity-related respiratory disease.

Evolution of Clinical Findings and Emerging Diagnostic Clues (Day 3–Day 5)

By the third day of life, the clinical course diverged from the expected trajectory of pulmonary hypertension associated with prematurity and respiratory distress syndrome. Oxygen requirement remained persistently high despite escalation of ventilatory and pharmacological support, and echocardiographic parameters continued to demonstrate markedly elevated pulmonary arterial pressures with limited hemodynamic improvement. Ventricular systolic function, although marginally improved, remained depressed relative to gestational age expectations, and right ventricular dilatation persisted. The patent ductus arteriosus remained small, with ongoing bidirectional shunting, without echocardiographic evidence of duct-dependent systemic or pulmonary circulation.

Repeat echocardiographic examination performed to reassess pulmonary hypertension revealed additional findings that were not apparent on initial studies. Increased echogenicity was noted along the walls of the main pulmonary artery and its proximal branches, extending beyond what would be expected from flow-related artifacts or technical factors. Similar hyperechogenic interfaces were observed adjacent to the descending aorta in suprasternal and parasternal views. Although these findings were initially subtle, their persistence across multiple imaging planes raised concern for an underlying arterial wall abnormality rather than transient hemodynamic change.

Systemic blood pressure measurements obtained serially during this period demonstrated values exceeding the 95th percentile for postnatal age and gestation. The emergence of sustained systemic hypertension was discordant with the presence of ventricular dysfunction and pulmonary hypertension and could not be readily attributed to inotropic therapy alone. Peripheral pulse examination revealed relative attenuation of upper limb pulses compared with lower limbs, without classical radiofemoral delay, further complicating the hemodynamic assessment. No clinical features suggestive of coarctation of the aorta were evident on echocardiography.

Laboratory evaluation was expanded to explore potential contributory factors. Inflammatory markers were elevated, prompting initiation of broad-spectrum antibiotics for suspected early-onset sepsis, although blood cultures remained sterile. Renal function parameters, including serum creatinine and urea, remained within age-appropriate reference ranges. Serum calcium concentrations were within normal limits; however, ionized calcium levels were elevated, and serum phosphorus levels were reduced. Parathyroid hormone concentrations were within the reference range, and no biochemical evidence of renal tubular dysfunction was identified. These metabolic findings, while not diagnostic, were atypical in the context of isolated pulmonary hypertension and prompted further consideration of systemic pathology. Relevant laboratory and biochemical parameters obtained during the early clinical course are summarized in Table 3.

Abdominal ultrasonography was performed as part of the evaluation for secondary causes of hypertension. This study revealed pronounced hyperechogenicity along the walls of the abdominal aorta and extending into the bilateral iliac arteries. The renal parenchyma appeared structurally normal, without evidence of nephrocalcinosis or renal artery stenosis. The presence of diffuse arterial wall echogenicity across multiple vascular territories suggested a generalized vascular process rather than a localized obstructive lesion. At this stage, the constellation of refractory pulmonary hypertension, emerging systemic hypertension, echogenic arterial walls on echocardiography and ultrasonography, and atypical mineral metabolism findings prompted reconsideration of the initial diagnostic framework and led to the pursuit of definitive cross-sectional vascular imaging. (Table 4)

Radiographic, Echocardiographic, and Cross-sectional Correlation

Serial chest radiography formed the earliest imaging modality to suggest that the clinical course was not solely attributable to parenchymal lung disease. The initial radiograph obtained shortly after admission demonstrated reduced lung volumes with diffuse reticulogranular opacities and prominent air bronchograms, in keeping with respiratory distress syndrome of prematurity. No focal consolidation, pneumothorax, or cardiomegaly was evident at this stage. Following surfactant administration, a repeat radiograph showed partial improvement in lung aeration; however, the degree of hypoxemia remained disproportionate to the radiographic lung findings.

On careful retrospective review of subsequent chest radiographs obtained during the first week of life, an unusual vascular pattern became apparent. Multiple linear, tubular, high-density opacities were seen tracking along expected mediastinal and paracardiac vascular pathways. These calcified structures extended vertically and obliquely within the thorax, paralleling the anatomical course of major vessels. The appearance created an initial visual impression ***resembling multiple intravascular catheters*** coursing through the mediastinum, despite the absence of corresponding central venous or arterial lines. (Figure 1) The density and continuity of these linear opacities, along with their bilateral and symmetric distribution, were inconsistent with medical devices and raised suspicion of intrinsic vascular wall pathology rather than extrinsic artifact.

Echocardiographic evaluation initially focused on assessment of pulmonary hypertension and myocardial function. Early studies confirmed markedly elevated pulmonary arterial pressures, bidirectional shunting across a small patent ductus arteriosus, and biventricular systolic dysfunction. As serial examinations were performed, increasing echogenicity of the

arterial walls became evident. Hyperechoic circumferential interfaces were noted along the main pulmonary artery, its proximal branches, and the descending aorta across multiple views. These findings persisted despite changes in hemodynamic status and imaging planes, arguing against flow-related phenomena or gain-dependent artifacts. No discrete intracardiac calcifications were identified, and valvular morphology remained normal. Serial echocardiographic findings and their progression over time are detailed in Table 2.

Abdominal ultrasonography provided further corroborative evidence of systemic vascular involvement. The abdominal aorta and bilateral iliac arteries demonstrated pronounced echogenic walls with posterior acoustic shadowing, consistent with calcification. The renal arteries also appeared echogenic along their course, although renal parenchymal echotexture was preserved, and corticomedullary differentiation remained intact. No nephrocalcinosis or renal artery stenosis was identified, and renal size was appropriate for gestational age.

Computed tomography angiography provided definitive characterization of the vascular abnormalities. (Figure 2) Non-contrast images revealed dense, circumferential calcification of the arterial walls involving the thoracic and abdominal aorta, pulmonary arteries, and multiple major branch vessels. The calcifications formed continuous, ring-like deposits along the internal elastic lamina, extending into the celiac axis, superior mesenteric artery, bilateral renal arteries, and iliac vessels. In the thorax and neck, similar calcific involvement was seen along the brachiocephalic, subclavian, and common carotid arteries. Despite the extensive calcific burden, contrast-enhanced angiographic reconstructions demonstrated preserved luminal patency without critical focal stenosis or occlusion. Subtraction and maximum-intensity projection images further delineated the diffuse arterial involvement, producing a characteristic vascular cast appearance while demonstrating sparing of intracranial arteries (Figure 3).

The combined imaging findings across modalities revealed a diffuse, multisystem arterial process with early radiographic manifestations preceding definitive cross-sectional diagnosis. The chest radiograph, in particular, served as an early but easily overlooked clue, with vascular calcifications masquerading as intravascular devices along central vascular trajectories. Recognition of this pattern, in conjunction with echocardiographic and ultrasonographic arterial wall echogenicity, was pivotal in prompting comprehensive vascular imaging and establishing the underlying diagnosis.

Table 1. Chronological Timeline of Clinical Events and Key Findings

Postnatal Day	Clinical Events	Key Findings
Day 0	Emergency LSCS for reduced fetal movements; immediate respiratory failure	Intubation at birth; severe hypoxemia
Day 0–1	Mechanical ventilation; surfactant administration	Chest radiograph: RDS with air bronchograms
Day 1	Initial echocardiography	Severe pulmonary hypertension; bidirectional PDA; biventricular dysfunction
Day 2	Escalation of cardiopulmonary support	Persistent hypoxemia; high FiO_2 requirement
Day 3	Repeat echocardiography	Persistent severe pulmonary hypertension; emerging arterial wall echogenicity
Day 4	Blood pressure monitoring	Sustained systemic hypertension
Day 4–5	Abdominal ultrasonography	Echogenic walls of abdominal aorta and iliac arteries
Day 6	CT angiography	Diffuse arterial wall calcification involving systemic and pulmonary vessels
Day 7	Respiratory improvement	Successful extubation to non-invasive support
Day 7 onwards	Targeted therapy initiated	Pamidronate; phosphate supplementation
Subsequent course	Genetic evaluation	Pathogenic ENPP1 variant identified

Table 2. Echocardiographic Findings Over Time

Parameter	Initial Study	Follow-up Studies
Pulmonary arterial pressure	Markedly elevated	Persistently elevated
Patent ductus arteriosus	Small; bidirectional shunt	Persistent bidirectional flow
Ventricular function	Depressed biventricular systolic function	Partial improvement
Right ventricular size	Dilated	Persistent dilation
Arterial wall appearance	No obvious abnormality	Progressive echogenicity of pulmonary artery and aorta

Table 3. Laboratory Parameters During Early Clinical Course

Parameter	Observed Trend
C-reactive protein	Elevated
Serum calcium	Within reference range
Ionized calcium	Elevated
Serum phosphorus	Reduced
Parathyroid hormone	Within reference range
Serum creatinine	Normal
Blood cultures	Sterile

Table 4. Key Features Prompting Diagnostic Reconsideration

Feature	Diagnostic Implication
Refractory pulmonary hypertension	Suggested non-parenchymal etiology
Early systemic hypertension	Inconsistent with isolated lung disease
Echogenic arterial walls on ultrasound	Indicative of arterial wall pathology
Linear vascular opacities on chest radiograph	Suggested vascular calcification
Diffuse arterial calcification on CT	Confirmed generalized arterial vasculopathy

Table 5. Published cases/series relevant to generalized arterial calcification of infancy/idiopathic infantile arterial calcification, contrasted with the index case (attached-library sources only).

Study (year)	Patient profile	Dominant presentation	Key diagnostic clue(s) on imaging	Genetic/etiologic note	Therapy reported	Outcome
Index case (present report)	Preterm/late preterm neonate; day-0 respiratory failure with differential saturations; early systemic hypertension	Severe hypoxemia/PPHN physiology with evolving systemic hypertension; multi-territory arterial calcification ultimately recognized	Calcified arterial "tracks" along multiple vascular beds on radiograph; CT angiogram showing extensive circumferential arterial wall calcification involving thoracic and abdominal aorta and major branches	ENPP1 mutation reported on whole-exome sequencing in shared clinical notes	Intensive cardiorespiratory support; pulmonary vasodilator strategy and antihypertensive escalation; bisphosphonate strategy	Early course complicated; follow-up/outcome to be finalized from clinical timeline and discharge status
Attia et al. (2015)[7]	Saudi female newborn; maternal polyhydramnios	Severe respiratory distress + systemic hypertension + PPHN	Emphasis on echogenic vessels on radiology as diagnostic trigger; large/medium artery calcifications highlighted as key finding	ENPP1 mutations positive; ENPP1 cited as mutated in many cases	NICU care + ventilation; supportive management	Death at ~5 months due to myocardial ischemia/cardiorespiratory arrest
Farquhar et al. (2005)[1]	Newborn (case report)	PPHN described as a primary feature; severe disease spectrum	Diagnosis established while on ECMO; pulmonary hypertension	Etiology discussed as likely autosomal recessive metabolic	ECMO support as pivotal bridge to diagnosis	Prognosis framed as high early mortality in historical cohorts

			singled out as unusual primary feature	disorder		
Varghese et al. (2024)[8]	Newborn with respiratory distress	Initial misdirection toward coarctation; later reclassified as GACI	Echocardiography suggested coarctation; CT demonstrated narrowing associated with GACI	Genetic basis implied (GACI described as genetic)	Early diagnosis and bisphosphonate treatment stated to improve survival	Not specified in excerpt; emphasis on diagnostic correction by CT
Brunod et al. (2018)[10]	Male infant	Severe early-onset hypertension refractory to multiple therapies	Renal Doppler showing diffuse echo-bright arteries; low-dose whole-body CT demonstrating extensive arterial calcifications	Novel homozygous ENPP1 mutation c.784A>G (p.Ser262Gly)	Four courses of bisphosphonates; calcifications decreased, HTN persisted	Alive at 24 months at time of report
Liu (Yunfeng) et al. (2021)[15]	Male preterm infant; presentation at ~2 months	Severe hypertension + seizures	Diffuse calcifications reported; clinical phenotype linked to ENPP1 variants	ENPP1 variants (c.130C>T and c.1112A>T) described; novelty claimed for one variant	Bisphosphonate + antihypertensive + anti-epileptic therapy	BP maintained 110–120/50–60 mmHg; neurodevelopmental concern anticipated
Bulfamante et al. (2021)	Newborn/infant (diagnostics/autopsy-confirmed case)	Severe diffuse early-onset arterial calcification phenotype	Diagnosis described as supported by clinical manifestations, imaging, histopathology and genetic tests; autopsy confirmation noted	Two heterozygous ENPP1 variants c.1412A>G (p.Tyr471Cys) and novel c.1715T>C (p.Leu572Ser)	Not specified in excerpt	Autopsy-confirmed GACI1; genotype–phenotype inference emphasized
Etidronate-treated survivor exemplar (2-year follow-up)	Severe GACI case diagnosed prenatally	Severe early phenotype; long-term management focus	Progressive resolution of arterial calcifications by 3 months; maintained through 2 years	ENPP1-linked severe case with novel homozygous missense mutation c.583T/C noted	IV pamidronate early → oral etidronate; monitoring for hypophosphatemia	Sustained radiologic improvement; mild hypophosphatemia due to renal phosphate wasting without rickets

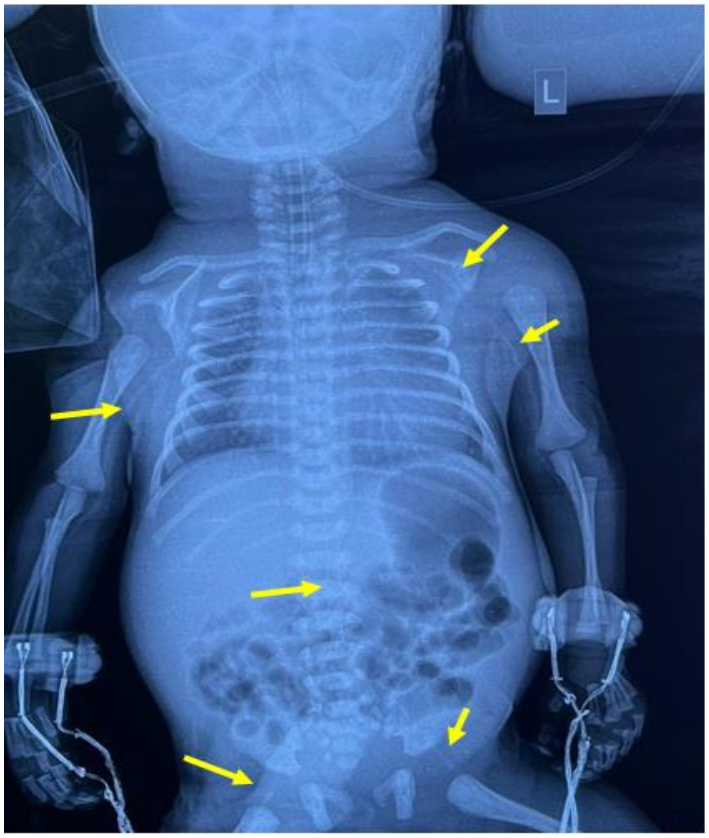

Figure 1. Plain radiograph demonstrating diffuse vascular calcification

Anteroposterior chest radiograph including upper limbs and abdomen demonstrating multiple linear, tubular, radio-opaque densities tracking symmetrically along the expected anatomical course of major arteries in the neck, thorax, upper limbs, and abdomen. These calcified vascular outlines impart an ***appearance mimicking multiple indwelling central venous catheters***,(yellow arrows) despite absence of corresponding intravascular devices. Lung fields show diffuse haziness consistent with respiratory distress syndrome, while the striking visibility of calcified arterial walls represents an early radiographic clue to an underlying systemic vascular pathology.

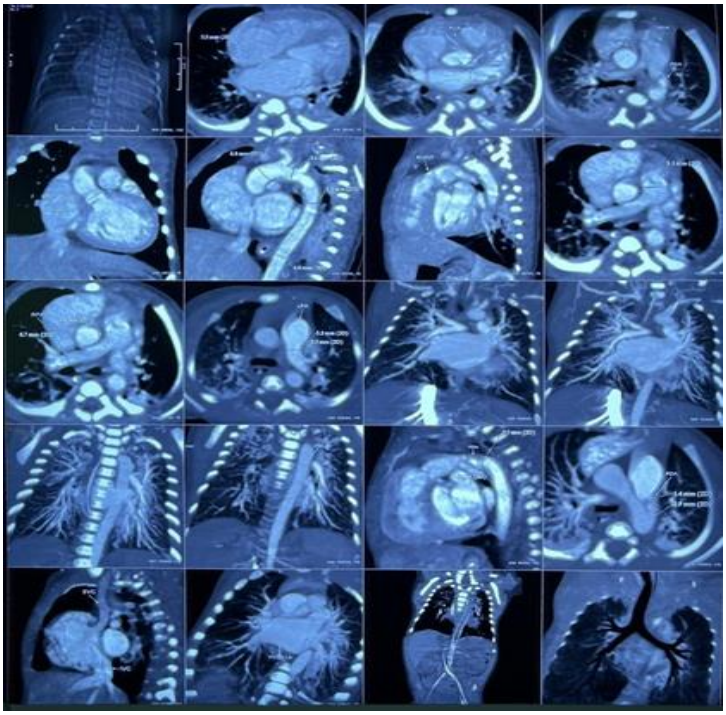

Figure 2. Contrast-enhanced CT angiography of thoracic and abdominal vasculature

Multiplanar reconstructed images from contrast-enhanced CT angiography showing extensive, circumferential arterial wall calcifications involving the thoracic aorta, abdominal aorta, main pulmonary artery, and multiple branch vessels. The calcifications are distributed along the arterial walls with relative preservation of luminal patency, without focal obstructive stenosis. Associated findings include dilated pulmonary arteries in keeping with severe pulmonary hypertension. These features confirm a diffuse arterial vasculopathy rather than focal congenital or inflammatory vascular disease.

Figure 3. CT angiographic subtraction images highlighting diffuse arterial involvement

Maximum-intensity projection and subtraction images from CT angiography delineating the widespread extent of arterial wall calcification across systemic and pulmonary circulations. Calcified arterial segments are visualized along the aorta and its major branches, producing a striking "vascular cast" appearance. Intracranial arteries are spared, and no renal parenchymal calcifications are identified. The imaging pattern is characteristic of generalized arterial calcification of infancy and provides definitive anatomic confirmation of the diagnosis.

DISCUSSION

Generalized arterial calcification of infancy (GACI), historically termed idiopathic infantile arterial calcification, is a rare and often fatal disorder characterized by extensive calcification of medium- and large-caliber arteries with associated intimal proliferation, leading to impaired vascular compliance and progressive cardiovascular compromise. [4] The disorder is now recognized as a genetic disease of ectopic mineralization, most commonly resulting from biallelic loss-of-function mutations in the ENPP1 gene, with ABCC6 mutations accounting for a smaller but significant subset of cases.[5] Advances in molecular characterization have reframed GACI as part of a broader phenotypic spectrum of ENPP1 deficiency, encompassing both early-onset arterial calcification and later manifestations such as autosomal recessive hypophosphatemic rickets.[3]

Previously reported cases of generalized arterial calcification of infancy with comparable clinical and imaging features are contrasted with the present case in Table 5. The clinical presentation of GACI is heterogeneous, with many affected infants presenting antenatally or in the immediate neonatal period with signs of circulatory compromise. Prenatal findings such as polyhydramnios, fetal distress, hydrops fetalis, and cardiomegaly have been repeatedly documented and are thought to reflect early vascular dysfunction and impaired fetal hemodynamics.[3] In the postnatal period, respiratory distress, heart failure, systemic hypertension, and feeding intolerance predominate, often mimicking more common neonatal cardiopulmonary conditions and contributing to diagnostic delay.[2]

Persistent pulmonary hypertension has emerged as a particularly important but under-recognized early manifestation of GACI. Although pulmonary hypertension is not traditionally emphasized in classic descriptions of the disease, several reports have documented severe, refractory pulmonary hypertension as a dominant presenting feature.[1,7] In these cases, pulmonary vascular calcification and arterial stiffening are believed to result in fixed elevation of pulmonary vascular resistance, rendering conventional vasodilator strategies less effective. The clinical course observed in the present case

closely parallels these reports, with pulmonary hypertension persisting despite optimized ventilatory support, surfactant therapy, and targeted pulmonary vasodilation.

Systemic hypertension is another hallmark feature frequently reported in neonatal GACI and is often severe, early-onset, and resistant to standard antihypertensive regimens.[2,7] The coexistence of pulmonary hypertension and systemic hypertension, as observed in this case, reflects the diffuse nature of arterial involvement and distinguishes GACI from isolated pulmonary vascular disorders. Similar hemodynamic profiles have been described in neonates initially misdiagnosed with coarctation of the aorta or primary cardiomyopathy before recognition of generalized arterial disease.[8]

Imaging plays a pivotal role in establishing the diagnosis of GACI, particularly when clinical features are nonspecific. While echocardiography is essential for assessing pulmonary pressures and ventricular function, its role in detecting arterial wall pathology is increasingly recognized. Progressive arterial wall echogenicity involving the pulmonary artery and aorta has been described as an early clue to underlying vascular calcification.[7] Abdominal ultrasonography may further demonstrate echogenic arterial walls involving the abdominal aorta and major branches, often with preservation of renal parenchymal architecture.[9]

Computed tomography angiography remains the definitive imaging modality for characterizing the extent and distribution of arterial calcification. Typical findings include circumferential, ring-like calcification along the internal elastic lamina of the aorta, pulmonary arteries, coronary arteries, and major systemic branches, frequently without critical luminal stenosis.[8,10] In the present case, CT angiography demonstrated extensive vascular involvement across thoracic, abdominal, and peripheral arterial territories, closely mirroring patterns reported in prior imaging-based case reports.

An important and under-appreciated observation in this case was the appearance of vascular calcifications on plain chest radiography. Linear, high-density opacities tracking along central vascular pathways created an appearance resembling multiple intravascular catheters, a phenomenon that has been described retrospectively in earlier reports but is seldom emphasized prospectively.[7] This finding underscores the potential value of meticulous review of routine radiographs, particularly when vascular silhouettes demonstrate abnormal density or continuity inconsistent with indwelling devices.

At the molecular level, ENPP1 deficiency leads to reduced extracellular inorganic pyrophosphate, a potent endogenous inhibitor of hydroxyapatite crystal formation.[11] Experimental models have demonstrated that systemic pyrophosphate deficiency alone is sufficient to induce widespread vascular calcification, providing a robust mechanistic basis for the arterial pathology observed in GACI. The identification of a pathogenic ENPP1 variant in this case aligns with the majority of reported neonatal cases and supports the current understanding of disease pathogenesis.[4]

Management of GACI remains challenging and controversial due to the absence of prospective trials and the rarity of the condition. Bisphosphonates, particularly etidronate and pamidronate, have been used empirically as pyrophosphate analogues to inhibit further calcification. Several case reports and small series have described stabilization or partial regression of vascular calcification with bisphosphonate therapy, particularly among infants who survive the early critical period.[12,13] However, spontaneous resolution of calcifications has also been documented, complicating interpretation of therapeutic efficacy.[2]

Prognosis in GACI is closely linked to the severity and distribution of vascular involvement. Mortality remains highest in the first six months of life, particularly in infants with pulmonary or coronary artery involvement.[3] Survivors may develop long-term sequelae, including persistent hypertension, cardiomyopathy, and skeletal manifestations related to hypophosphatemia, reinforcing the concept of ENPP1 deficiency as a lifelong multisystem disorder rather than an isolated neonatal condition.[3,14]

In summary, this case adds to the growing body of literature emphasizing that refractory pulmonary hypertension, early systemic hypertension, and subtle vascular imaging abnormalities should prompt consideration of generalized arterial calcification of infancy. The diagnostic trajectory observed—progressing from presumed pulmonary pathology to recognition of a diffuse arterial disease—closely parallels previously reported cases and highlights the importance of integrating clinical, imaging, and genetic data. Early recognition remains essential for informed prognostication, targeted management, and genetic counseling, particularly in a disorder with significant early mortality and evolving therapeutic possibilities.

LEARNING POINTS / KEY MESSAGES

- Severe pulmonary hypertension that is disproportionate to the degree of parenchymal lung disease and refractory to standard therapy should prompt evaluation for rare neonatal vasculopathies.
- The coexistence of pulmonary hypertension and early-onset systemic hypertension in a neonate suggests diffuse arterial involvement rather than isolated cardiopulmonary pathology.

- Linear, high-density vascular opacities on plain chest radiography, particularly when tracking along expected arterial courses and mimicking intravascular devices, may represent early radiographic evidence of arterial wall calcification.
- Progressive arterial wall echogenicity on echocardiography and ultrasonography across multiple vascular territories should raise suspicion for a generalized arterial calcification disorder.
- Computed tomography angiography is essential for definitive delineation of disease extent, demonstrating characteristic circumferential arterial calcification with relative preservation of luminal patency.
- Early genetic confirmation enables accurate diagnosis, informs prognosis, and supports multidisciplinary management and family counseling in disorders of ectopic vascular mineralization.

CONCLUSION

This case demonstrates how a rare, diffuse arterial disorder can initially masquerade as common neonatal cardiopulmonary pathology, with persistent pulmonary hypertension serving as the dominant early manifestation. Careful attention to discordant clinical features, subtle but progressive imaging abnormalities, and evolving hemodynamic patterns enabled recognition of a unifying vascular etiology. The observations underscore the diagnostic value of meticulous radiographic review and comprehensive vascular imaging in neonates with refractory pulmonary hypertension and systemic hypertension. Early identification of generalized arterial calcification of infancy is critical for guiding management, prognostication, and genetic evaluation in a condition associated with high early morbidity and mortality.

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