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Hypercholesterolemic valvulopathy and severe atherosclerosis in paediatric patients

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Brief Report

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Abstract

Background: Atherosclerosis is the leading cause of vascular disease worldwide, and traditionally it has been considered a disease of older individuals. However, this atherosclerotic process begins early in childhood, and when exposed to critically high levels of atherogenic risk factors, coronary artery disease may develop even during childhood. There are very few reports of coronary artery disease in young children, and most are linked to Kawasaki disease and congenital coronary abnormalities. Involvement of the mitral valve due to hypercholesterolaemia is rare and under-reported. *Methods:* We did a retrospective audit of all children (age <14 years) who underwent coronary angiogram between January 2005 and July 2024 in our tertiary care hospital. Only those children with atherosclerotic coronary artery disease were included. *Results:* We studied four paediatric cases of atherosclerotic coronary artery disease with concomitant valvular involvement despite ongoing lipid-lowering therapy. We highlight the mechanisms of valvular involvement and the challenges to the diagnosis and treatment of familial hypercholesterolaemia. *Conclusions:* These cases highlight the cardiovascular changes associated with this "malignant" atherosclerosis and emphasise the need for early recognition and prompt initiation of aggressive lipid-lowering therapy at diagnosis.

Introduction

Familial hypercholesterolaemia, an inherited metabolic disorder, is caused by a low-density lipoprotein receptor abnormality.[1] It is characterised by delayed low-density lipoprotein clearance, with ensuing severe hypercholesterolaemia and subsequent vascular and peripheral manifestations. While the occurrence of coronary artery disease and involvement of the aortic valve and ascending aorta due to atherosclerosis in these individuals is well established,[1,2,3,4] involvement of the mitral valve has been sparsely reported.[1,4]

As per the World Health Organization, India accounts for one-fifth of the worldwide deaths due to cardiovascular disease. The majority of these studies describe coronary artery disease with respect to the conventional risk factors. There are very few reports of coronary artery disease[6] and valvular pathology[2] resulting from familial hypercholesterolaemia among Indians. A prior study indicates that familial hypercholesterolaemia contributes to 15% of the incident coronary artery disease burden in adult Indian patients.[6]

Our report describes involvement of the coronary arteries, aortic valve, ascending aorta, descending thoracic aorta, and the mitral valve due to atherosclerotic deposits.

Materials and methods

We did a retrospective audit of all children (age <14 years) who underwent coronary angiogram between January 2005 and July 2024 in our tertiary care hospital. As per our institutional policy, individuals below 14 years of age are classified as paediatric patients. Accordingly, angiographic records of all patients younger than 14 years were identified and included in the analysis. Institutional review board approval was obtained. Eight eligible patients were identified. Coronary artery disease due to atherosclerosis[7,8] was included, and other aetiologies such as Kawasaki disease, Takayasu's disease, and coronary anomalies were excluded after applying relevant diagnostic criteria for these conditions.[9,10]

Angiographic lesion quantification was done using visual assessment. Over the past two decades, several diagnostic criteria for vascular disorders have been proposed. To simplify case selection and maintain consistency, we applied the most recent diagnostic criteria to exclude patients with alternative aetiologies such as Kawasaki disease and Takayasu arteritis, as noted above. With regard to imaging protocols, all angiographic procedures were performed using Philips catheterisation systems that have remained unchanged in both laboratories for the past 25 years. Specific data on the echocardiography machines used were not available; however, there were no changes in diagnostic or imaging protocols during the study period that would have affected data ascertainment.

Case 1

A 12-year-old girl presented with a history of xanthomas on her knees since age 5 and hypercholesterolaemia (TC 780, LDL 630). She was diagnosed with homozygous familial hypercholesterolaemia and previously started on statins, which she had discontinued. She now had exertional chest pain, nocturnal angina, and one episode of syncope requiring Cardiopulmonary resuscitation (CPR). Both parents had heterozygous familial hypercholesterolaemia. On examination, she had xanthomas on both knees and her right elbow (Figure 1). Her lipid profile showed TC 470 mg/dL, TG 59 mg/dL, HDL 23 mg/dL, and LDL 417 mg/dL. Genetic testing revealed an Low density Lipoprotein - Receptor (LDL-R) mutation (5' splice site on intron 4; detailed genetics report is in the Supplementary Data). Echocardiogram revealed severe mitral regurgitation, mild aortic regurgitation, and post-ductal coarctation of the aorta (gradient 52 mmHg), with diffuse intimal thickening in the aorta. The ejection fraction was 58%. Coronary angiography showed 70% stenosis in the obtuse marginal branch of the left circumflex artery, with minor lesions in other vessels (Figure 1). A peripheral angiogram indicated non-flow-limiting stenosis of the left subclavian artery, with no significant gradient from the aortic root to the femoral artery.

Case summary

The patient described above had genetically confirmed homozygous familial hypercholesterolaemia, classified as "Definite" according to established diagnostic criteria.[11] Genetic analysis revealed an ***LDLR*** mutation, and she exhibited evidence of atherosclerotic involvement of both coronary and peripheral arteries, along with a family history of premature coronary artery disease. Previous studies have suggested that long-term statin therapy is associated with a 50% reduction in the risk of developing aortic stenosis, and up to a 95% reduction in the risk of supravalvular aortic stenosis.[3]

Additionally, she had severe mitral regurgitation with a non-dilated left ventricle and coarctation of the aorta. Guideline-directed medical therapy was initiated, and cascade screening of family members was undertaken. She remains under clinical follow-up, with her first review visit pending.

Case 2

A 7-year-old boy presented with yellowish-brown skin lesions on his left forearm and buttocks, starting at 2 years of age. After a normal lipid profile analysis, he was diagnosed with juvenile xanthogranuloma and advised to follow up. He again presented at 8 years of age, with a 4-year history of progressive skin lesions which now involved his hands and inner canthi of both eyes. His lipid profile then showed a total cholesterol of 700 mg/dl, triglycerides of 191 mg/dl, low-density lipoprotein of 600 mg/dl, and high-density lipoprotein of 31 mg/dl. He was started on statins and ezetimibe but was lost to follow-up and returned at age 14 with exertional dyspnoea (NYHA class 2). At this visit, his lipid profile showed total cholesterol of 680 mg/dl, high-density lipoprotein of 27 mg/dl, low-density lipoprotein of 546 mg/dl, and triglycerides of 131 mg/dl. An echocardiogram revealed severe supravalvular aortic stenosis (Figure 2), mild aortic regurgitation, and calcific aortic valve leaflets, while a catheterisation showed a gradient of 50 mmHg from across the stenosis and an ostioproximal Left anterior descending artery (LAD) stenosis.

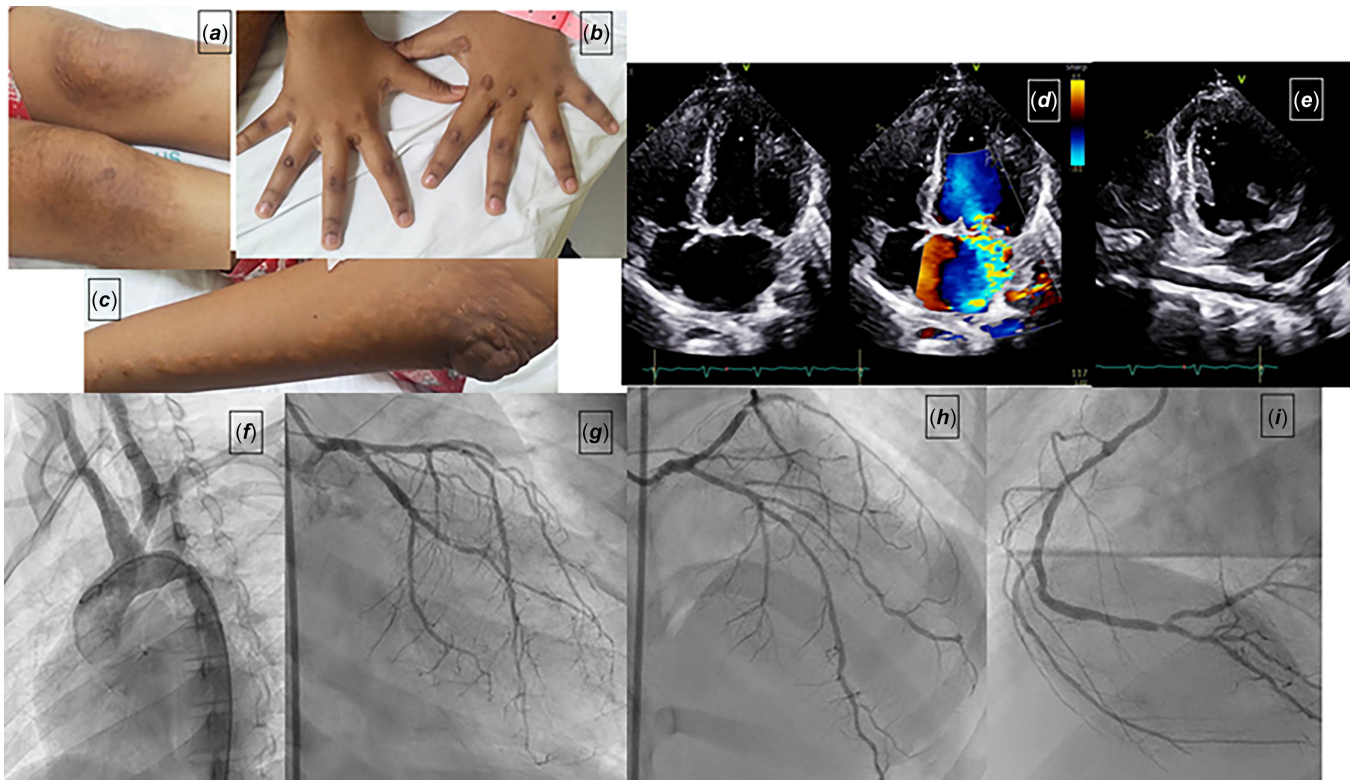

Figure 1. Clinical, echocardiographic, and angiographic findings of Case no 1. Legend: ***a***,***b***,***c*** - Xanthomatous deposits in the knees (***a***), dorsum of the hands (***b***) and left elbow (***c***); ***d*** - Severe mitral regurgitation with posteriorly directed jet. Bright echogenic IVS and valves due to lipid deposition; ***e*** - Diffuse intimal thickening in descending thoracic aorta and Abdominal Aorta, with bright echogenic appearance due to cholesterol deposition; ***f*** - Post ductal Coarctation of the aorta (CoA); ***g***,***h***, ***i*** - Angiograms; Diffuse CAD in the Lcx (***g***), LAD (***h***), and the RCA (***i***).

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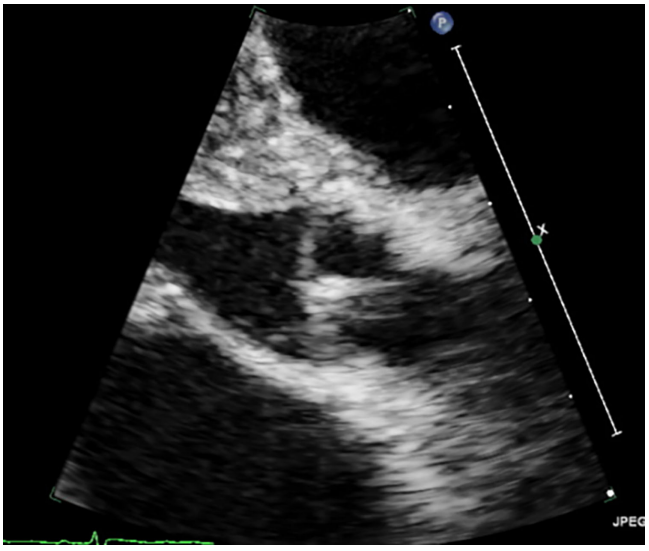

Figure 2. Supravalvular ridge, with calcific aortic valve leaflets.

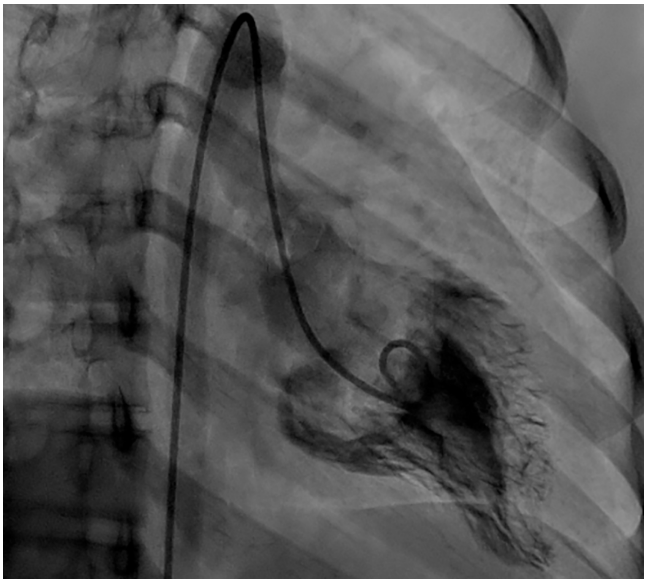

Figure 3. Aortic root angiogram showed diffuse narrowing of aortic root, with cath gradient of 68 mmHg.

Case summary

Supravalvular aortic stenosis is a generalised disease of the arterial wall, caused by a thickening of the media or intima layers, causing a narrowing of the lumen of the involved arteries. It typically affects branches of the pulmonary and coronary arteries,[12] whereas cerebral circulation, descending aorta, renal arteries, and other aortic tributaries are commonly spared. In total, 70% of patients of supravalvular aortic stenosis are associated with Williams–Beuren syndrome.[13] Association with familial hypercholesterolaemia is a rare occurrence.[14]

Our patient described above did not have syndromic features, except tuberous xanthomas as mentioned. Hypercholesterolaemia here was familial in the homozygous form.[14] We proceeded with family and cascade screening. He was started on aggressive lipid-lowering therapy and referred for surgical resection of the supravalvular ridge with Coronary artery Bypass grafting (CABG) surgery (grafts to LAD and Right Coronary Artery (RCA)). He was admitted elsewhere 10 days later with Non ST Elevation Myocardial Infarction (NSTEMI), underwent CABG, but died during the post-operative period (history was as per the child's father; records were unavailable)

Case 3

A 14-year-old girl presented with exertional dyspnoea lasting one year. Previously diagnosed with supravalvular aortic stenosis, she underwent balloon aortic valvotomy at age 13 and was treated for hyperlipidaemia with rosuvastatin. Her mother had heterozygous familial hypercholesterolaemia. Re-evaluation revealed hyperlipidaemia (TC 609, HDL 25, TG 123) and xanthomatous deposits on her left elbow. Echocardiography showed aortic wall thickening from the annulus to the supravalvular region (12 mm) (Figure 3), normal ascending aorta, mild aortic regurgitation, and normal trileaflet aortic valves.

CAG showed occluded LAD and an occluded RCA.

We made a diagnosis of supravalvular aortic stenosis, double vessel coronary artery disease, and homozygous familial hypercholesterolaemia.

She was initiated on aggressive lipid-lowering therapy and underwent CABG (LIMA-> LAD, pedicled RIMA-> PDA) + Doty's repair of aorta (bovine pericardial patch).

Intraoperative findings showed extensive plaque and atheroma with areas of calcification in the proximal ascending aorta and root.

Case 4

A 7-year-old male presented with exertional angina (NYHA class 2) and dyspnoea, referred from dermatology due to eruptive xanthomas from hyperlipidaemia. Examination revealed arcus senilis and xanthomas on his knees, buttocks, and elbows. Cardiac examination noted a pansystolic murmur.

Blood tests showed TC 809, TG 113, HDL 30, and LDL 694, despite being on prior statin therapy for three years. His echocardiogram showed severe mitral regurgitation and mild aortic stenosis. Coronary angiogram revealed 95% ostial Left Main Coronary Artery (LMCA) stenosis and 80% proximal LAD stenosis, with left ventricular angiogram confirming severe mitral regurgitation and normal left ventricular function. He experienced bradycardic arrest post-procedure but was revived. His parents refused a bailout Percutaneous Coronary Intervention (PCI).

He was started on aggressive lipid-lowering and antianginal therapy, and referred for CABG and mitral valve repair. This child died from an out-of-hospital cardiac arrest (OHCA) after 1 year with an LDL value of 900 mg/dl (as per the telephonic details obtained from the father). This case points to familial hypercholesterolaemia (likely homozygous), critical left main and single-vessel coronary artery disease, severe mitral regurgitation from extensive atherosclerosis, and mild aortic stenosis. Images (from 2005) are not available.

Discussion

In our series, all four patients had homozygous familial hypercholesterolaemia, with involvement of the mitral and aortic valves in varying degrees. Three of them (Cases 1-3) had supravalvular

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aortic stenosis, all non-syndromic. A summary of the four patients reported is shown in Table 1.

Hypercholesterolaemic valvular heart disease

Atherosclerosis affecting the aortic valve—leading to valvular and supravalvular aortic stenosis in young children with familial hypercholesterolaemia—has been described in various reports previously.[15] In the post-statin era, homozygous familial hypercholesterolaemia has reportedly been diagnosed at a mean age of 20.3 years.[15]

The reason for preferential cholesterol deposition on the aortic valve is not fully understood. Proposed mechanisms include shear stress-induced inflammation triggered by high concentrations of oxidised lipids, leading to fibrosis, calcification, and remodelling.[15] Aortic regurgitation has been described as the earliest feature of Aortic Valve (AV) disease.[16]

Over time, vascular tissues in the vicinity of the aortic root are affected. Involvement of the sino-tubular junction leads to coronary ostial involvement, with ensuing coronary artery disease. Ascending aortic disease leads to calcification, ridging, and shrinkage of the supravalvular aortic ridge, with post-stenotic dilatation[17] and reduced distensibility,[16] ultimately resulting in supravalvular aortic stenosis.

Involvement of the mitral valve from this "malignant" atherosclerosis has been reported in a few reports previously.[4,18] Possible mechanisms of mitral regurgitation in the context of extensive atherosclerosis include mitral annular calcification, direct extension from aortic atherosclerosis, and silent subclinical ischaemia of the papillary muscles, among others.[4]

Challenges in the diagnosis and treatment of familial hypercholesterolaemia

Awareness regarding familial hypercholesterolaemia remains low. As a result, the condition is often underdiagnosed and undertreated. Despite being more prevalent, heterozygous familial hypercholesterolaemia remains undiagnosed in up to 90% of cases.[15] Several factors contribute to this, including the absence of national cholesterol screening programmes—particularly universal paediatric screening for familial hypercholesterolaemia—limited access to genetic testing,[19] and the lack of uniform, systematic diagnostic criteria. Barriers to effective therapy include underdiagnosis, limited availability of newer lipid-lowering therapies, and restricted access to lipoprotein apheresis.[19]

How cardiovascular disease in familial hypercholesterolaemia patients differs from that in adults with traditional risk factors

Cardiovascular disease in patients with familial hypercholesterolaemia is postulated to differ from cardiovascular disease driven by traditional risk factors such as obesity, acquired dyslipidaemia, and smoking. Valvular dysfunction in familial hypercholesterolaemia patients tends to occur at a younger age and often precedes the development of coronary artery disease, unlike in non-familial hypercholesterolaemia patients.[16] Aortic valve lesions in familial hypercholesterolaemia originate from the ascending aortic side rather than the left ventricular side, similar to what is seen in senile calcific aortic stenosis.[16] Importantly, calcific aortic stenosis may develop in familial hypercholesterolaemia patients regardless of statin therapy, and often does not respond to statins.[7,8] Concerning mitral valve disease, an earlier report has postulated a pathophysiological similarity to vascular atherosclerosis.[18] However, large case series supporting this observation are currently lacking. A table summarising previously reported cases of mitral regurgitation (MR) in patients with familial hypercholesterolaemia (FH) is outlined in Table 2.

The influence of traditional ischaemic heart disease risk factors in adults with familial hypercholesterolaemia has been previously studied. Notably, factors such as age >40 years, systemic hypertension, elevated lipoprotein(a) levels, and a positive family history of cardiovascular disease have been shown to correlate with an increased incidence of coronary artery disease.[20] In contrast, coronary artery disease severity appears to correlate poorly with LDL cholesterol (LDL-C) levels or the presence of *LDLR* mutations.[20]

Implications from our study

Coronary and aortic valve pathologies relating to familial hypercholesterolaemia-associated extensive atherosclerosis in the first

Table 1. Summary of the four reported patients

	CAD	Valvular lesions	Diseases of the Aorta and the Aortic Arch.	Age at diagnosis	TC	TG	HDL	LDL	Present status
Case no 1	+	+	+	At age 5[a,b]	780	N/A	N/A	632	Alive
		MR	CoA	At age 12[c]	470	59	23	419	
Case 2	+	+	+	At age 2[a]	Normal[d]	Normal[d]	Normal[d]	Normal[d]	Deceased
		AR, MR	Supravalvular AS	At age 8[b]	700	191	31	600	
				At age11[c]	680	131	27	546	
Case 3	+	+	–	At age14 [c]	609	123	25	511	Unknown
		MR							
Case 4	+	+	+	At age 4[a,b]	910	149	89	562	Deceased
		MR, AS, AR	Supravalvular AS	At age 7[c]	809	113	30	694	

CAD = Coronary artery disease; VHD = Valvular heart disease; MR = Mitral regurgitation; AR = Aortic regurgitation; AS = Aortic stenosis; CoA = Coarctation of the aorta; TC = total cholesterol; TG = Triglycerides; HDL = high-density lipoproteins; LDL = low density lipoproteins; N/A = not available.
[a]Indicates the age at which the first diagnosis of hyperlipidaemia was made.
[b]Lipid profile values without lipid-lowering therapy.
[c]Lipid profile values On Lipid-lowering therapy.
[d]Reported as normal in the medical records; exact numerical values were not available.

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Table 2. Table summarising previously reported cases of mitral regurgitation (MR) in patients with familial hypercholesterolaemia (FH)

	Total sample size (n)	FH type	Incidence of cohort who had MR	Severity of MR	Age in years	LDL level in mg/dl	Combined Aortic and mitral disease	Concomitant CAD
Akito Kawaguchi et al.[1]	39	HeFH	16	Grade 1, $n = 12$ Grade 2, $n = 4$	47.4 ± 7.4	144 ± 36	6	N/A
Akl C Fahed et al.[4]	21	HoFH	6	Mild MR, $n = 4$ Moderate MR, $n = 2$	Range 19–65	Mean 447	21	3
Kathiravan et al.[22]	1	N/A	1	Severe	11	657	1 (Moderate AR)	N/A
Rajamannan et al.[18]	1	N/A	1	N/A	7	951 (TC)	N/A	N/A

FH = Familial Hypercholesteroaemia; CAD = Coronary artery disease; MR = Mitral regurgitation; TC = total cholesterol; LDL = low density lipoproteins; N/A = not available.

two decades of life, though underreported, have been documented. The incidence and staging of the associated mitral valve disease—as well as its response to treatment and prognosis—have not been established and merit detailed study.

Limitations of our study include its single-centre, retrospective design, with case data being ascertained long after the index hospitalisation in three of the four cases. Outcome details were primarily obtained through telephonic conversations with the patients' fathers, given the emotional discomfort they experienced in recounting events surrounding deaths that had occurred well before the initiation of this study (Cases 2 and 4). Additional limitations include the small sample size and incomplete documentation of diagnostic evaluations performed prior to inclusion in this study.

Future directions

The survival rates of patients with familial hypercholesterolaemia have improved since the introduction of statin therapy. Calcific aortic stenosis is the leading cause of morbidity and mortality among these patients. Additionally, two of our patients exhibited severe mitral regurgitation. As mitral valve involvement and subsequent regurgitation are uncommon, it is essential to investigate the prognostic implications of these cases further.

There is a clear need for large, multicentre familial hypercholesterolaemia registries, particularly in India and other South Asian countries, to better characterise the homozygous familial hypercholesterolaemia phenotype, treatment responses, and long-term outcomes in these populations. Further research is also warranted to develop cost-effective screening strategies and sustainable management protocols tailored to resource-limited settings, especially in light of evolving global health challenges. Based on our observations, we recommend that all patients with confirmed homozygous familial hypercholesterolaemia undergo echocardiographic evaluation at diagnosis, followed by serial assessments every 1–2 years.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951125109244.

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Competing interests. None to declare.

Ethical standards. This retrospective case series was approved by the institutional review board Min no 2408138. The requirement for informed consent was waived due to the retrospective nature of the study, and all data were anonymised to ensure patient confidentiality.

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