Missed case of fever of unknown origin during COVID-19 pandemic: patent ductus arteriosus endarteritis

Akash Batta , Samman Verma , Prashant Panda , Yash Paul Sharma

Cardiology, PGIMER, Chandigarh, India

Correspondence to
Dr Prashant Panda; prashantpanda85@gmail.com

Accepted 13 May 2021

SUMMARY

A 40-year-old woman presented with fever of unknown origin (FUO) for 2 months. Without a definitive diagnosis and having received multiple empirical antibiotics from outside without relief, she was referred to our centre. Cardiac auscultation was remarkable for a grade 3/6 continuous murmur in the upper left sternal border. Echocardiogram revealed a patent ductus arteriosus (PDA) and a 5×7 mm mobile vegetation at the pulmonary artery bifurcation. Blood culture grew *Streptococcus* mutans. Embolisation of the vegetation to the pulmonary circulation occurred after the start of intravenous antibiotics resulting in fever relapse. Antibiotics were continued for 6 weeks and the fever settled. She underwent device closure of PDA after 12 weeks and is currently doing fine. Infective endocarditis/endarteritis is an important differential in a patient of FUO. A thorough clinical examination is important in every case of FUO, gives an important lead into diagnosis and guides appropriate investigations to confirm it.

BACKGROUND

Patent ductus arteriosus (PDA) compromises 5%–10% of congenital heart defects and is symptomatic in 0.5/1000 live births.[1] While most patients present during infancy or childhood, rarely small to even moderate PDAs may be well tolerated, with only years of chronic volume overload leading to congestive heart failure in adulthood.[2] It is even rarer for PDA to present with infective endarteritis in adults. This case report highlights this unusual presentation, emphasises the need for a detailed evaluation of a patient presenting with fever of unknown origin (FUO) and illustrates the role of echocardiography in conjunction with other imaging modalities for gauging the full extent of infective endarteritis in PDA.

CASE PRESENTATION

At the peak of the COVID-19 pandemic in our region, a 40-year-old woman without any comorbidities was referred to our hospital as a case of FUO. She had a history of high-grade fever on and off for the past 2 months. During her evaluation at outside hospitals, various blood and radiological investigations were carried out, but no aetiology could be found. She was empirically given oral antibiotics (azithromycin, ciprofloxacin, amoxycillin intermittently for 5–10 days each) for a total duration of 6 weeks without a response. During initial teleconsultation services at our centre because of COVID-19, workup on the lines of FUO was carried out.

But with little lead into her diagnoses, she was called to our medicine outpatient department for a physical evaluation. On initial examination at our centre, her blood pressure was 136/62 mm Hg, pulse rate was 110 beats/minute, saturation was 98% on room air, respiratory rate was 18 breaths/minute and the temperature was 102.0°F. Pallor was present, however, no icterus, clubbing or peripheral lymphadenopathy was noted. A grade 3/6 continuous murmur was best audible in the upper left sternal border. There were no peripheral stigmata of infective endocarditis such as splenomegaly, Janeway lesions, Osler nodes, Roth spots or splinter haemorrhages.

INVESTIGATIONS

Her initial laboratory analysis revealed anaemia (haemoglobin of 97 g/L), normal total leucocyte count and negative peripheral blood smear, normal renal and hepatic function tests, normal urinalysis and negative urine and blood cultures (four pairs), negative rheumatoid factor, negative widal and HIV serology, negative skin test for tuberculosis. Her inflammatory markers erythrocyte sedimentation rate (73 mm in the first hour) and C reactive protein (33.1 mg/L) were raised. The chest X-ray (CXR) was normal. Reverse transcription-PCR for COVID-19 was negative five times over the last 2 months.

Her ECG revealed Q waves in I and avL and evidence of left ventricular hypertrophy (figure 1). After the findings on physical examination, a transthoracic echocardiogram (TTE) was carried out. It showed a 6 mm PDA and a 5× 7 mm mobile echogenic mass just proximal to the bifurcation of the pulmonary artery, where the PDA jet struck the pulmonary artery (figure 2; videos 1 and 2). There was a left-to-right shunt across PDA with a peak gradient of 54 mm Hg and an end-diastolic gradient of 28 mm Hg. The mean pulmonary artery pressure was 24 mm Hg.

DIFFERENTIAL DIAGNOSIS

At the onset, a long list of differential diagnoses was kept including various infections most notably tuberculosis and HIV, rheumatological disorders given that she was a middle-aged woman, and neoplastic disorders were also considered. However, after the physical examinations had revealed a continuous murmur, the list narrowed and the possibility of

To cite: Batta A, Verma S, Panda P, *et al*. *BMJ Case Rep* 2021;**14**:e243727. doi:10.1136/bcr-2021-243727

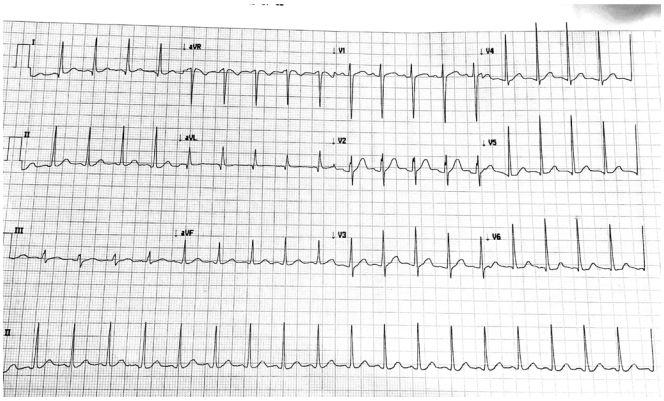


Figure 1 12-Lead ECG showing Q waves in I and avL and evidence of left ventricular hypertrophy.

infective endocarditis in the background of PDA or a ruptured sinus of Valsalva rupture or aortopulmonary window or peripheral pulmonary stenosis was kept. All the above-listed conditions can present with a continuous murmur.

TREATMENT

She was admitted the same day. As repeated prior blood cultures were sterile, we decided to stop all antibiotics and repeated four pairs of blood cultures over the next 48 hours. Cultures were negative in 24-hour incubation, but subsequently, two pairs grew *Streptococcus* mutans on delayed incubation, sensitive to ceftriaxone, levofloxacin and vancomycin. As the case now fulfilled the modified Duke's criteria, a diagnosis of infective endocarditis was made, and she was started on intravenous ceftriaxone+vancomycin. Fever spikes reduced and she improved clinically by day 5 of the start of intravenous antibiotics.

On the seventh day of her admission, she developed new-onset pleuritic left-sided chest pain and there was a resurgence of fever spikes up to 101.0°F. A CXR showed mild bilateral pleural effusion and repeat TTE could not localise the vegetation previously identified (figure 3A; video 3). Suspecting pulmonary embolism of the vegetation, CT pulmonary angiogram was done. The same did not show any evidence of thromboembolism but revealed a pseudoaneurysm in the posterior septal branch of the left descending pulmonary artery with adjacent patchy lung consolidation and nodule in the left lower lobe and also in the right middle lobe (figure 3B). Positron emission tomography (PET) scan showed Fluorodeoxyglucose (FDG) avid parenchymal nodules in the right upper lobe and fibro-consolidatory changes in bilateral lower lobe (figure 3C). It also showed non-FDG avid

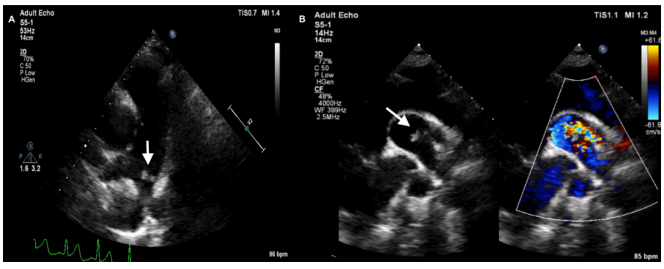
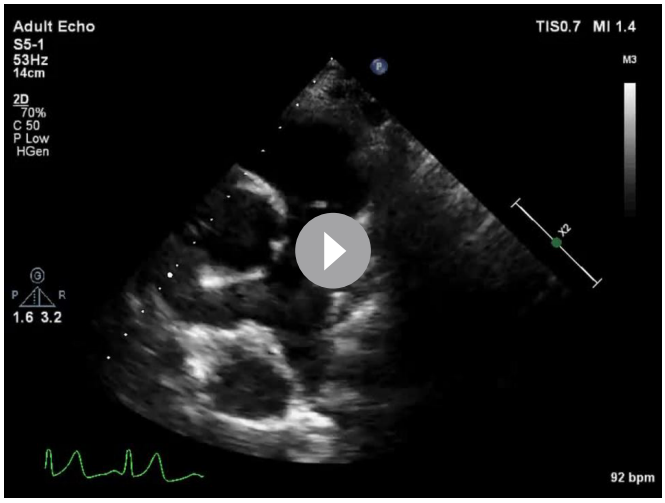


Figure 2 Two-dimensional transthoracic echocardiogram showing the vegetation (white arrows) near the pulmonary artery bifurcation in short axis (A) and suprasternal views (B). Colour jet of patent ductus arteriosus can be visualised (B).



Video 1 Two-dimensional transthoracic echocardiogram in parasternal short axis showing mobile vegetation attached to pulmonary artery near bifurcation.

parenchymal ground-glass opacities in the right upper and left lower lobes.

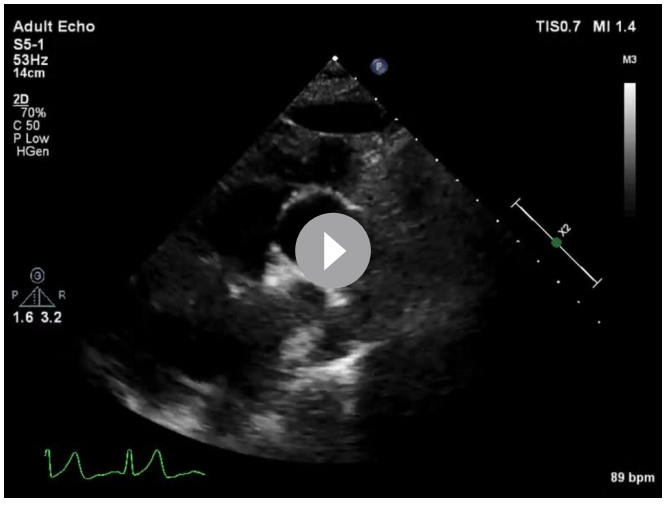
Antibiotics were continued and the fever settled in another 4 days. The patient became afebrile by day 12 of admission and remained so thereafter. She was given vancomycin for 14 days after which only ceftriaxone was continued.

OUTCOME AND FOLLOW-UP

After her discharge on day 14, she completed 6 weeks of intravenous antibiotics via a day-care facility. Subsequently, she underwent PDA device closure after 12 weeks. Currently, she is asymptomatic at 6 months of follow-up.

DISCUSSION

The ductus arteriosus develops from the sixth aortic arch and forms a connection between the main pulmonary artery and the descending aorta, 5–10 mm distal to the origin of the left subclavian artery.[3] It usually closes in two phases, functional closure by 12 hours and anatomical closure by 2–3 weeks. Patency beyond



Video 2 Two-dimensional transthoracic echocardiogram in suprasternal view showing patent ductus arteriosus and a mobile vegetation attached to pulmonary artery.

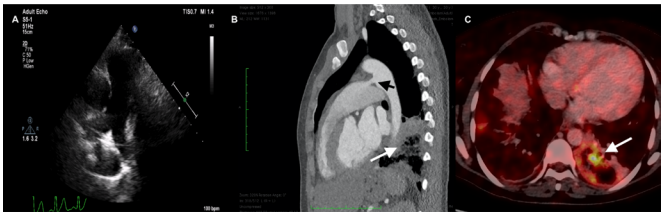
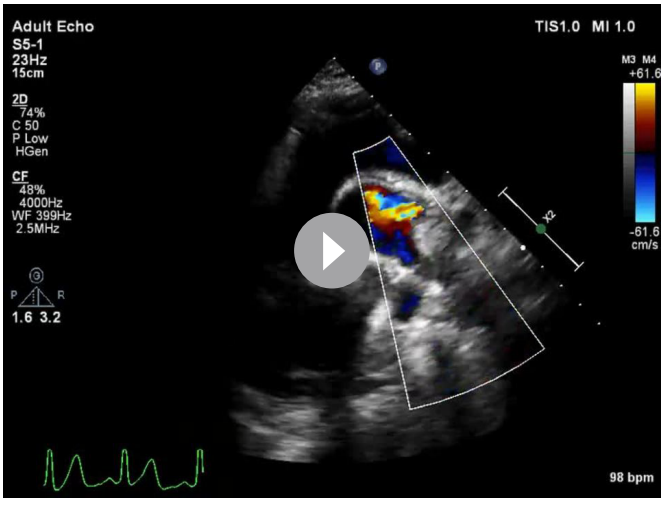


Figure 3 Post embolisation images of two-dimensional transthoracic echocardiogram showing no vegetation that was seen previously (A). CT images showing patent ductus arteriosus (black arrow). Consolidation in left lower lobe is apparent on both CT (B) and fluorodeoxyglucose positron emission tomography (C) (white arrows) images.

a few weeks is considered abnormal. The age of presentation and the magnitude of shunting depends on an interplay of three factors, namely the dimensions of the PDA, the pressure difference between the aorta and the pulmonary artery, and the systemic and pulmonary vascular resistance. As a corollary, the natural history of a patient with PDA varies from asymptomatic, incidental detection to frank congestive heart failure.[2 4] Physical examination often reveals a continuous machinery murmur in the upper left sternal border. The murmur typically starts with the first heart sound, peaks with the second heart sound and fades by the end of diastole. A diastolic rumble may also be present with increased flows.[2]

Infective endarteritis is the most common cause of death in PDA in the paediatric population, with a 20%–45% fatality rate.[5] The incidence of PDA endarteritis is extremely low in children>4 years old.[6] Its incidence has declined of late with the advent of routine surgical closure, dental care and antibiotic use.[5] However, third world countries still have a higher incidence. Vegetations are commonly found in the pulmonary end of the ductus owing to increased turbulence and consequent endothelial injury in the same location, and embolisation occurs more commonly to the pulmonary than systemic circulation.[5 7]

Infective endarteritis can be diagnosed using Duke's criteria based on clinical features, blood cultures, echocardiography and CT/PET scan. *Staphylococcus* and *Streptococcus* are the most commonly isolated organisms, but about 10% of the cases are culture negative.[8] TTE has high sensitivity and negative predictive value for diagnosing infective endarteritis, but vegetations may not be easily visualised, especially in adults. Transoesophageal echocardiogram can detect the same more reliably.[9]



Video 3 Post embolisation images of two-dimensional transthoracic echocardiogram showing no vegetation that was seen previously, but only the jet of patent ductus arteriosus seen when colour is applied.

Patient's perspective

Due to the COVID-19 pandemic at the time of my illness last year, I could not get proper medical attention and that lead to a delay in diagnosing my illness. I was surprised to hear that I had congenital heart disease since childhood as I never had any symptoms. Thanks to the doctors and God's grace, I was able to overcome the illness.

Learning points

- Infective endocarditis/endarteritis is an important differential in a patient with fever of unknown origin (FUO).
- A thorough clinical examination is important in every case of FUO, gives an important lead into diagnosis and guides appropriate investigations to confirm it.
- Inappropriate use of empirical antibiotics is the most common cause of culture-negative endocarditis, and identifying microbiological agent is at the heart of successful management of endocarditis.
- Careful echocardiographic assessment of all cardiac structures should be done and not limited to the cardiac valves in the case of FUO.

Other complications of PDA include heart failure, which is more common in moderate to large PDAs with volume overload. Large non-restrictive PDAs are prone to develop irreversible hypertensive pulmonary vascular disease.[10] Another rare complication is the aneurysm of the ductus arteriosus which is reported in up to 8% of PDAs. It can present with mass effects such as compression of the recurrent laryngeal nerve or left bronchus or as heart failure if very large.[2 11]

Patients with infective endarteritis in PDA are usually treated with 2–6 weeks of intravenous antibiotics, depending on the organism isolated and its antibiotic sensitivity.[12] Every attempt should be made to get a microbiological diagnosis,empirical antimicrobials should be based on the clinical setting and consultation with an infectious disease specialist should be obtained before treatment initiation.[13] PDA closure is indicated for patients with evidence of left ventricular volume overload and no pulmonary artery hypertension regardless of symptoms. Device closure is the preferred method for PDA closure, with surgical closure limited to patients with too large a duct or anatomy unfavourable for device closure, such as aneurysm formation.[12]

Contributors AB: Conceptualisation, methodology, investigation, supervision, original draft preparation, reviewing and editing. SV: Original draft preparation, reviewing and editing. PP: Conceptualisation, methodology, investigation, supervision, validation, original draft preparation, reviewing and editing. YPS: Supervision, reviewing and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Akash Batta http://orcid.org/0000-0002-7606-5826
Samman Verma http://orcid.org/0000-0003-1536-2429
Prashant Panda http://orcid.org/0000-0002-2420-5209

REFERENCES

1 Saxena A, Relan J, Agarwal R, *et al*. Indian guidelines for indications and timing of intervention for common congenital heart diseases: revised and updated consensus statement of the Working group on management of congenital heart diseases. *Ann Pediatr Cardiol* 2019;12:254.
2 Schneider DJ, Moore JW. Patent ductus arteriosus. *Circulation* 2006;114:1873–82.
3 Deshpande P, Baczynski M, McNamara PJ. *Patent ductus arteriosus: the physiology of transition*. Elsevier, 2018: 225–31.
4 Rudolph AM, Drorbaugh JE, AULD PA, *et al*. Studies on the circulation in the neonatal period. The circulation in the respiratory distress syndrome. *Pediatrics* 1961;27:551–66.
5 Sadiq M, Latif F, Ur-Rehman A. Analysis of infective endarteritis in patent ductus arteriosus. *Am J Cardiol* 2004;93:513–5.
6 Rushani D, Kaufman JS, Ionescu-Ittu R, *et al*. Infective endocarditis in children with congenital heart disease: cumulative incidence and predictors. *Circulation* 2013;128:1412–9.
7 Choi K-N, Yang T-H, Park B-S, *et al*. A case with patent ductus arteriosus complicated by pulmonary artery endarteritis. *J Cardiovasc Ultrasound* 2008;16:90–2.
8 Habib G, Lancellotti P, Antunes MJ, *et al*. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of cardiology (ESC). endorsed by: European association for Cardio-Thoracic surgery (EACTS), the European association of nuclear medicine (EANM). *Eur Heart J* 2015;36:3075–128.
9 Jacob S, Tong AT. Role of echocardiography in the diagnosis and management of infective endocarditis. *Curr Opin Cardiol* 2002;17:478–85.
10 Espino-Vela J, Cardenas N, Cruz R. Patent ductus arteriosus. with special reference to patients with pulmonary hypertension. *Circulation* 1968;38:V–45.
11 Kanabar K, Batta A, Debi U, *et al*. Large ductus arteriosus aneurysm in an elderly patient. *IHJ Cardiovascular Case Reports* 2019;3:115.
12 Baumgartner H, De Backer J, Babu-Narayan SV, *et al*. 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J* 2021;42:563–645.
13 Baddour LM, Wilson WR, Bayer AS, *et al*. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. *Circulation* 2015;132:1435–86.