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

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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. 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. 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, amoxyccillin 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 trans-thoracic 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
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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 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
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. 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.

Infective endarteritis is the most common cause of death in PDA in the paediatric population, with a 20%–45% fatality rate. The incidence of PDA endarteritis is extremely low in children>4 years old. Its incidence has declined of late with the advent of routine surgical closure, dental care and antibiotic use. 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. 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. 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.

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. 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.

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. 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. 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.

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.
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