Haemophilus parainfluenzae endocarditis presenting with symptoms of COVID-19

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SUMMARY
A young man presented early in the UK’s second COVID-19 pandemic surge with a twelve-day history of fever, dry cough, breathlessness, myalgia and loss of smell and taste. His chest X-ray showed bilateral ground-glass opacities. He was treated for COVID-19 pneumonitis but covered for bacterial infection with antibiotics. He developed shock and respiratory failure, requiring vasopressors and continuous positive airway pressure. He improved but experienced transient visual disturbances and headache. Nasopharyngeal swabs and antibody tests for COVID-19 were negative. Blood cultures grew Haemophilus parainfluenzae. A new murmur prompted an echocardiogram. This confirmed a large, mobile mitral valve vegetation. An MRI of the brain showed bilateral embolic infarcts. He underwent urgent mitral valve repair and made an excellent recovery. Whether COVID-19 caused his presenting symptoms or facilitated the bacteraemia remains unclear. It seems more likely that infective endocarditis masqueraded as COVID-19. Clinicians should be aware of how context of the pandemic can bias diagnostic reasoning.

BACKGROUND
With a varied and often insidious clinical course, infective endocarditis (IE) can be difficult to diagnose but incidence is increasing globally, even in low-risk individuals. Streptococci, Staphylococci and Enterococci together comprise over 90% of culture-positive IE. 8.5% is caused by organisms often found in the blood, which rarely attack cardiac valves (eg. Pseudomonas species). The remaining 1.5% is caused by oral and respiratory tract commensal organisms that rarely enter the circulation but are tropic to valve tissue when they do. These are the HACEK organisms (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens and Kingella species). Haemophilus parainfluenzae is the most common, causing one third of HACEK IE. In comparison to non-HACEK IE, HACEK organisms tend to affect younger people (often with no cardiac history) and carry a higher risk of haemorrhagic stroke but a better overall prognosis. Diagnosing HACEK IE is notoriously challenging, with only one third of cases confirmed within 4 days of hospital admission.

This case reminds us to consider IE in patients with sepsis and signs of reduced cardiac output. It highlights some classic features of HACEK IE and the value of blood cultures drawn prior to antibiotic administration. The clinical course also raises fascinating questions as to whether COVID-19 caused this patient’s original symptoms, facilitated the H. parainfluenzae bacteraemia or biased clinical assessment and management.

CASE PRESENTATION
A young man was brought by ambulance to the emergency department (ED) of a district general hospital early in the UK’s second COVID-19 pandemic surge. He had a 12-day history of fever, dry cough, exertional breathlessness, light headedness, myalgia, fatigue, reduced appetite and loss of smell and taste. He described chest ‘tightness’, headache, photophobia, visual disturbances, vomiting and diarrhoea. He had no known COVID-19 contacts but had visited a UK city 2 days prior to becoming unwell. A nasopharyngeal COVID-19 swab collected 5 days into his illness had returned ‘indeterminate’.

He was deteriorating at home and called NHS 111, which triggered an ambulance call-out. Paramedics found him to be tachypnoeic, tachycardic, hypotensive and febrile (respiratory rate: 20 breaths/min, SpO2: 96% on air, heart rate: 124 beats/min, blood pressure (BP): 101/62 mmHg, temperature: 39.2°C).

He had a history of seborrhoeic dermatitis and multiple tooth extractions 13 years previously. He had never smoked or used intravenous drugs.

In ED he was persistently febrile and became more hypotensive (BP: 71/40 mmHg) but maintained saturations of 95% on air. On examination he had increased work of breathing and bilateral lung crepitations. He was cyanotic and peripherally shut down with a capillary refill time of 4 seconds and dry mucous membranes. Auscultation revealed no heart murmur.

INVESTIGATIONS
An arterial blood gas (ABG) on air confirmed type-one respiratory failure (pH: 7.45, partial pressure of oxygen (pO2): 4.9 kPa, partial pressure of carbon dioxide (pCO2): 4.0 kPa, SpO2: 93%, lactate: 1.6 mmol/L). An electrocardiogram (ECG) showed sinus rhythm with right axis deviation (figure 1). A chest X-ray (CXR) was reported as extensive, bilateral ground-glass opacification with mid and lower zone predominance (figure 2), concerning for COVID-19 pneumonitis but potentially suggestive of pulmonary oedema.

He had raised inflammatory markers (C-reactive protein (CRP): 247 mg/L, white cell count (WCC): 15.9×10⁹/L, neutrophil count: 14.6×10⁹/L) but a lymphopenia (lymphocyte count: 0.4×10⁹/L), normocytic anaemia (haemoglobin: 123 g/L, mean
cell volume: 82.3 fL) and thrombocytopenia (platelet count: 129×10^9/L). He was also hyponatraemic (Na: 127 mmol/L). There were no prior baseline renal function tests for comparison but creatinine and urea were probably raised given his slim build (creatinine: 82 µmol/L, urea: 7.5 mmol/L). Liver function tests were also mildly deranged (alanine transaminase: 57 IU/L, bilirubin: 21 µmol/L, alkaline phosphatase: 96 IU/L). A D-dimer was raised (845 ng/mL). A urine dip showed a trace of blood but was negative for leucocytes and nitrites. Blood cultures were taken.

His hypotension was refractory to fluid resuscitation. A bedside echocardiogram in ED showed no evidence of right heart failure, although views were suboptimal. Valves were not assessed.

A repeat ABG on oxygen at 15 L/min via non re-breathe mask showed severe type-one respiratory failure (pH: 7.43, pO_2: 8.8 kPa, pCO_2: 4.4 kPa).

Nasopharyngeal swabs for COVID-19 PCR on day 12 and day 14 of symptoms were negative, as was COVID-19 antibody serology on day 13.

A CXR on day 3 of admission showed worsening bilateral mid and lower zone patchy shadowing and upper lobe diversion (figure 3).

On day 5 of admission, blood cultures returned positive for *H. influenzae* (sensitive to co-amoxiclav and tetracyclines). This was later amended to *H. parainfluenzae*.

A loud pansystolic murmur prompted a formal echocardiogram. This revealed a large, friable, mobile mass (1.5×1.5 cm) on the anterior mitral valve leaflet causing torrential mitral regurgitation (figures 4 and 5).

A computed tomography (CT) scan of the chest, abdomen and pelvis (figure 6) showed bilateral pleural effusions with atelectasis and lower lobe ground-glass densities but no evidence of distant emboli.

Magnetic resonance imaging (MRI) of the brain on day 9 of admission was used to investigate recurrent episodes of right frontal headache and visual disturbance (figure 7). This showed
small foci of restricted diffusion in the supratentorial brain parenchyma bilaterally, suggestive of embolic infarcts.

A repeat MRI of the brain for similar symptoms postoperatively showed resolution of these lesions but new microhaemorrhages in the left thalamus, right parietal lobe and possibly the left superior frontal white matter.

DIFFERENTIAL DIAGNOSIS

This previously healthy, young man presented in shock. Determining the type of shock was the initial priority. The presenting symptoms, including the cardinal symptoms of COVID-19, and bilateral CXR changes were considered consistent with a respiratory viral syndrome. This prompted a working diagnosis of septic shock with COVID-19 pneumonitis.

However, the examination findings could suggest a state of reduced cardiac output such as distributive or cardiogenic shock. When his blood pressure failed to improve, a bedside echo helped rule out cardiac decompensation from tamponade or a large pulmonary embolism.

CRP trended steeply down with initial therapy, but the leucocytosis and lymphopenia persisted. CRP began climbing again from day 8 of admission, which could have suggested an ongoing source of infection, although he remained afibrile on antibiotics and his overall clinical state improved.

His transient right frontal headache and visual disturbances, including a black shadow over the right visual field, continued, although there was no focal deficit at the time of neurological examination.

On day 8 of admission, he complained of intermittent left lateral chest discomfort. This, alongside the unusual blood culture result, rising inflammatory markers and transient neurological symptoms prompted a repeat examination. This revealed a loud pansystolic murmur and a splinter haemorrhage. A formal echocardiogram confirmed the diagnosis of mitral valve IE. Reassessment of the blood culture samples confirmed *H. parainfluenzae*. The same organism was later identified on intraoperative tissue samples sent for 16S PCR.

TREATMENT

Initial treatment included oxygen via a non re-breathe mask, liberal intravenous fluid resuscitation and antibiotics. COVID-19 pneumonitis was treated with dexamethasone, remdesivir and intermediate-dose dalteparin thromboprophylaxis. Intravenous co-amoxiclav and clarithromycin were soon escalated to piperacillin and tazobactam.

Over the first 3 days he required continuous positive airway pressure and intermittent vasopressor support with peripheral metaraminol on ICU. He improved and, by day 7, was weaned off oxygen and mobilising well.

Once *H. parainfluenzae* was confirmed, antibiotics were changed to ceftriaxone (2g twice daily) and the isolate reported to Public Health England.
The echocardiogram findings, recurrent neurological symptoms and MRI evidence of cerebral emboli prompted an urgent interhospital transfer for cardiac surgery. He underwent mitral valve repair on day 12 of admission (figures 8 and 9). Postoperative blood cultures were negative.

An echocardiogram 5 days post-operatively confirmed good placement of the annuloplasty ring, no mitral regurgitation and mildly impaired left and right ventricular systolic function.

He completed a further 6 weeks of postoperative intravenous ceftriaxone on advice of the microbiology team. He was also commenced on aspirin, omeprazole and low-dose bisoprolol.

**OUTCOME AND FOLLOW-UP**

He made an excellent recovery, suffering no persisting neurological deficit. He continues to experience self-resolving visual disturbances (floaters and shadows) for which neither ophthalmologists or stroke physicians are convinced of a vascular or embolic cause. He awaits a neurology opinion as to whether these could represent migraineous auras. He returned to work. An echocardiogram 3 weeks post-operatively confirmed a well-functioning mitral valve (figures 10 and 11). He was followed-up 6 weeks post discharge in cardiology and cardiac surgical clinics.

**DISCUSSION**

Most septic patients are intravascularly depleted and require fluid resuscitation. However, this case highlights pulmonary oedema and cardiogenic shock as important differential diagnoses in patients who remain hypotensive or become increasingly hypoxic following fluid resuscitation. The combination of sepsis and cardiogenic shock should raise suspicion of IE.

This case demonstrates some key features of HACEK IE. In comparison to non-HACEK IE, it takes longer to diagnose, affects younger people and those with no history of cardiac disease, and carries a higher risk of stroke and intracranial haemorrhage. Mitral valve HACEK IE is particularly associated with stroke. The course of HACEK IE is classically considered insidious. However, this case mirrors other reports of *H. parainfluenzae* acting aggressively in previously healthy people.

This patient’s dental history was his only risk factor for IE. However, this detail came to light only after the diagnosis was made. Physicians rarely delve into dental histories and community dental work rarely appears on general practitioner
COVID-19 prevalence should affect how diagnostic tests are interpreted, although this is a challenge in practice when prevalence is changing rapidly. Tests for diseases with a high prevalence carry a lower negative predictive value and, therefore, a higher chance of false negatives. COVID-19 prevalence was relatively low when this patient presented (only one COVID-19 positive patient was admitted in our hospital at the time). In this context, a negative swab result is more reliable; so stronger clinical suspicion is needed to continue to treat for COVID-19.

Learning points

- Infective endocarditis is a rare but important differential diagnosis in patients with infection and signs of reduced cardiac output or cardiogenic shock.
- Neurological symptoms in the context of infection can suggest an embolic process.
- Haemophilus parainfluenzae is the most common HACEK organism to cause endocarditis and can form large mitral valve vegetations.
- H. influenzae can act in an aggressive manner to cause shock in young, healthy people.
- Clinicians should be astute to diagnostic framing bias and base rate neglect as the pretest probability of COVID-19 infection changes with pandemic surges.

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