ESC European Society of Cardiology

European Heart Journal - Case Reports (2021) **5**(6), 1–7
doi:10.1093/ehjcr/ytab201

GRAND ROUND
Heart failure

Anakinra treats fulminant myocarditis from *Neisseria meningitidis* septicaemia and haemophagocytic lymphohistiocytosis: a case report

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Received 2 February 2021; first decision 22 March 2021; accepted 30 April 2021

Background Fulminant myocarditis is a life-threatening condition characterized by acute cardiac dysfunction requiring pharmacological or mechanical circulatory support. Haemophagocytic lymphohistiocytosis (HLH) is an uncommon state of immune dysregulation and overactivation. Inflammation mediated by interleukin-1 (IL-1) is thought to play a role in the pathogenesis of myocarditis and HLH, and there is some evidence that the IL-1 receptor antagonist Anakinra may play a role in treating both these conditions.

Case summary A 26-year-old previously healthy male presented to the Emergency Department with a 3-day history of malaise, headache, vomiting, diarrhoea, and fever. He was profoundly hypotensive on arrival, diagnosed with septic shock, and commenced on broad-spectrum antibiotics and vasopressors. Blood tests showed lymphopenia, thrombocytopenia, low fibrinogen and elevated high sensitivity troponin T, ferritin, and C-reactive protein. Echocardiography demonstrated severely impaired biventricular systolic function and a diagnosis of fulminant myocarditis was made. His condition deteriorated and he required intubation and additional inotropic support. A diagnosis of HLH was made and he was commenced on Anakinra and Methylprednisolone. His condition improved rapidly thereafter. Polymerase chain reaction testing subsequently confirmed infection with *Neisseria meningitidis*.

Discussion In this case, fulminant myocarditis and HLH were life-threatening manifestations of meningococcal septicaemia, and the patient's condition improved rapidly following administration of the IL-1 receptor antagonist Anakinra. These complications should be borne in mind in septic patients with marked haemodynamic instability and multiorgan dysfunction, and treatment with Anakinra should be considered in those who fail to respond to conventional therapy.

Keywords Myocarditis • Neisseria meningitidis • Sepsis • Anakinra • Case report

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Handling Editor: Ching-Hui Sia
Peer-reviewers: Andriana Anagnostopoulou; Filipe Penna De Carvalho and Mark Abela
Compliance Editor: Bretty Sydney Bernstein
Supplementary Material Editor: Christian Fielder Camm

Learning points

- Fulminant myocarditis and haemophagocytic lymphohistiocytosis (HLH) may be life-threatening manifestations of meningococcal septicaemia, and should be considered in all patients with this disease who have marked haemodynamic instability and multiorgan dysfunction.
- Interleukin-1-mediated inflammation is likely to play a key role in the pathogenesis of fulminant myocarditis and HLH associated with sepsis.
- Anakinra may be a valuable treatment in critically unwell patients with this disease.

Primary specialities involved other than cardiology

Rheumatology, Intensive Care Medicine, Infectious Diseases.

Introduction

Fulminant myocarditis is a life-threatening condition characterized by the acute onset of myocardial inflammation and contractile dysfunction necessitating pharmacological or mechanical circulatory support.[1] The condition has myriad underlying aetiologies, including viral and bacterial infection, drugs, toxins, and autoimmune and inflammatory disorders.[2] Evidence is emerging of the role of interleukin-1 (IL-1) in the pathogenesis of myocarditis, and there is some evidence that inhibition of IL-1 signalling may improve outcomes in these patients.[3]

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon state of immune dysregulation and overactivation. IL-1 plays an important role in the pathogenesis of HLH[4] and IL-1 receptor antagonists have shown success in treating this condition.[5]

We present a case of fulminant myocarditis secondary to *Neisseria meningitidis* septicaemia complicated by HLH, which was successfully treated with the recombinant, non-glycosylated human monoclonal IL-1 receptor antagonist Anakinra.

Timeline

Day 0	Presented to the Emergency Department with a 3-day history of malaise, headache, vomiting, diarrhoea, and fever. Shocked on arrival
	Diagnosed with sepsis of unknown aetiology, commenced on Piperacillin/Tazobactam and Noradrenaline and admitted to the intensive care unit
	Bloods on admission showed lymphopenia, thrombocytopenia, low fibrinogen and elevated high sensitivity troponin T, ferritin, and C-reactive protein
Day 1	Echocardiography performed on account of high vasopressor requirements, demonstrating severely impaired biventricular systolic function
	Diagnosis of fulminant myocarditis secondary to sepsis made
	Intubated for worsening type I respiratory failure
	Antibiotics changed to Clindamycin, Meropenem, Doxycycline, and Gentamicin
	Commenced on continuous venovenous haemofiltration (CVVHF) for oliguric acute kidney injury
	Dobutamine and Levosimendan started on account of worsening haemodynamic status
Day 2	Presumptive diagnosis of haemophagocytic lymphohistiocytosis made; HScore 166
	Commenced on Methylprednisolone and Anakinra
Day 4	Marked improvement in haemodynamic and respiratory status
	Extubated
	Urine output returned and CVVHF stopped
Day 9	Stepped down to the ward
	Polymerase chain reaction on blood at the national reference laboratory detected *Neisseria meningitidis* serotype W135
	Bone marrow aspirate was reported as showing haemophagocytosis
Day 15	Cardiovascular magnetic resonance (CMR) imaging demonstrated prolonged native myocardial T1 and T2 relaxation times in mid-anterior and lateral myocardial walls suggesting myocarditis with subtle midwall fibrosis in the same areas. Biventricular function had normalized by this time
Day 18	Discharged home
6 months	Asymptomatic and returned to normal life
	Follow-up CMR showed reduction in left ventricular mass to normal values, near-normalization of biventricular function and complete resolution of T1, T2, and late gadolinium enhancement abnormalities
15 months	Remained asymptomatic and able to carry out all physical activities without limitation

Case presentation

A 26-year-old male presented to the Emergency Department of our tertiary care hospital, prior to the beginning of the COVID-19 pandemic, with a 3-day history of general malaise, headache, vomiting, diarrhoea, and fever. On arrival at the hospital, he collapsed and was found to be profoundly hypotensive (blood pressure 70/40 mmHg). On physical examination, he appeared unwell with a temperature of 39.4°C but there were no specific findings; in particular no rash, cardiac murmurs, splinter haemorrhages, or signs of meningism.

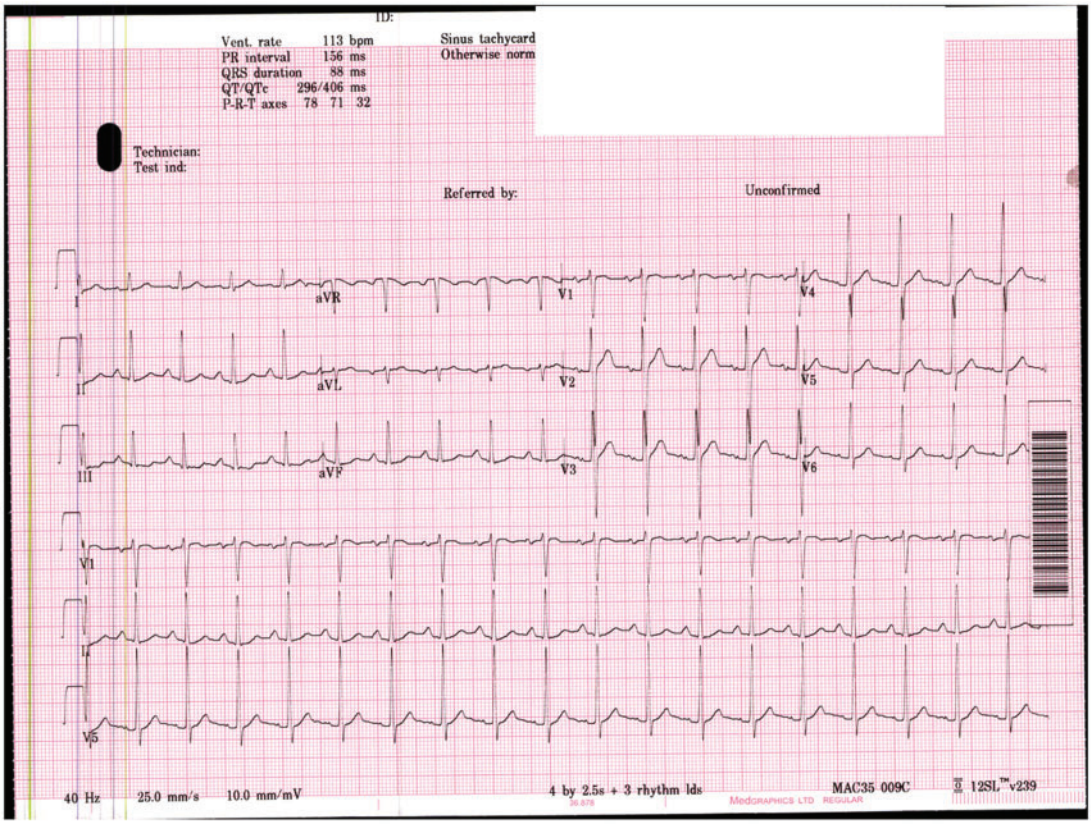
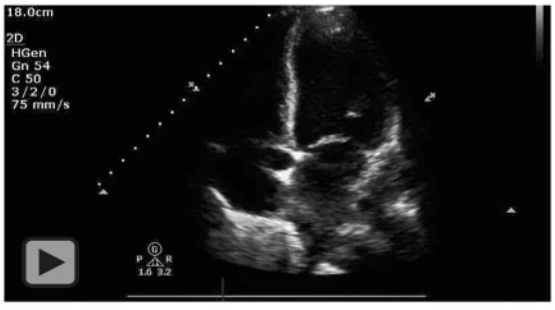


Figure 1 Electrocardiogram obtained on admission to hospital demonstrated sinus tachycardia.

The patient was usually fit and well with no past medical history and took no regular medications. There was no family history of note. He lived with his two sisters and worked in information technology. He drank alcohol occasionally, did not smoke and denied use of recreational drugs. He had travelled to Gambia around 6 months prior to the presentation and to Russia 1 month previously.

The patient was provisionally diagnosed with sepsis of unknown aetiology and was resuscitated with intravenous fluids and given Piperacillin/Tazobactam as a broad-spectrum antibiotic. He remained persistently hypotensive with raised serum lactate and an infusion of Noradrenaline was commenced and he was admitted to the intensive care unit (ICU).



Video 1 A transthoracic echocardiogram obtained on admission showed global severely impaired biventricular systolic function. Parasternal long-axis view then apical four-chamber view.

Initial investigations

Samples of blood, sputum, stool, and urine were obtained for culture, antigen testing, serology, and molecular genetic testing for common bacterial and viral pathogens.

The admission full blood count was remarkable for thrombocytopenia (platelet count 77×10^9/L, normal range 140–400 $\times 10^9$/L) and lymphopenia (0.21×10^9/L, normal range 1.0–4.0 $\times 10^9$/L). The haemoglobin was within the normal range. The thrombocytopenia worsened over the next 3 days reaching a nadir of 16×10^9/L. The admission fibrinogen was low (1.2 g/L, normal range 1.6–3.8 g/L) and the prothrombin time prolonged (23 s, normal range 9–12 s) without the use of anticoagulants. The ferritin (1636 µg/L, normal range 30–340 µg/L) and high sensitivity C-reactive protein (CRP) (116 mg/L, normal range < 5 mg/L) were elevated, as was the high sensitivity troponin T (685 ng/L, normal range < 14 ng/L) and aspartate aminotransferase (AST, 309 units/L, normal range 10–50 units/L). The triglyceride level was normal (1.0 mmol/L, normal range < 2.3 mmol/L).

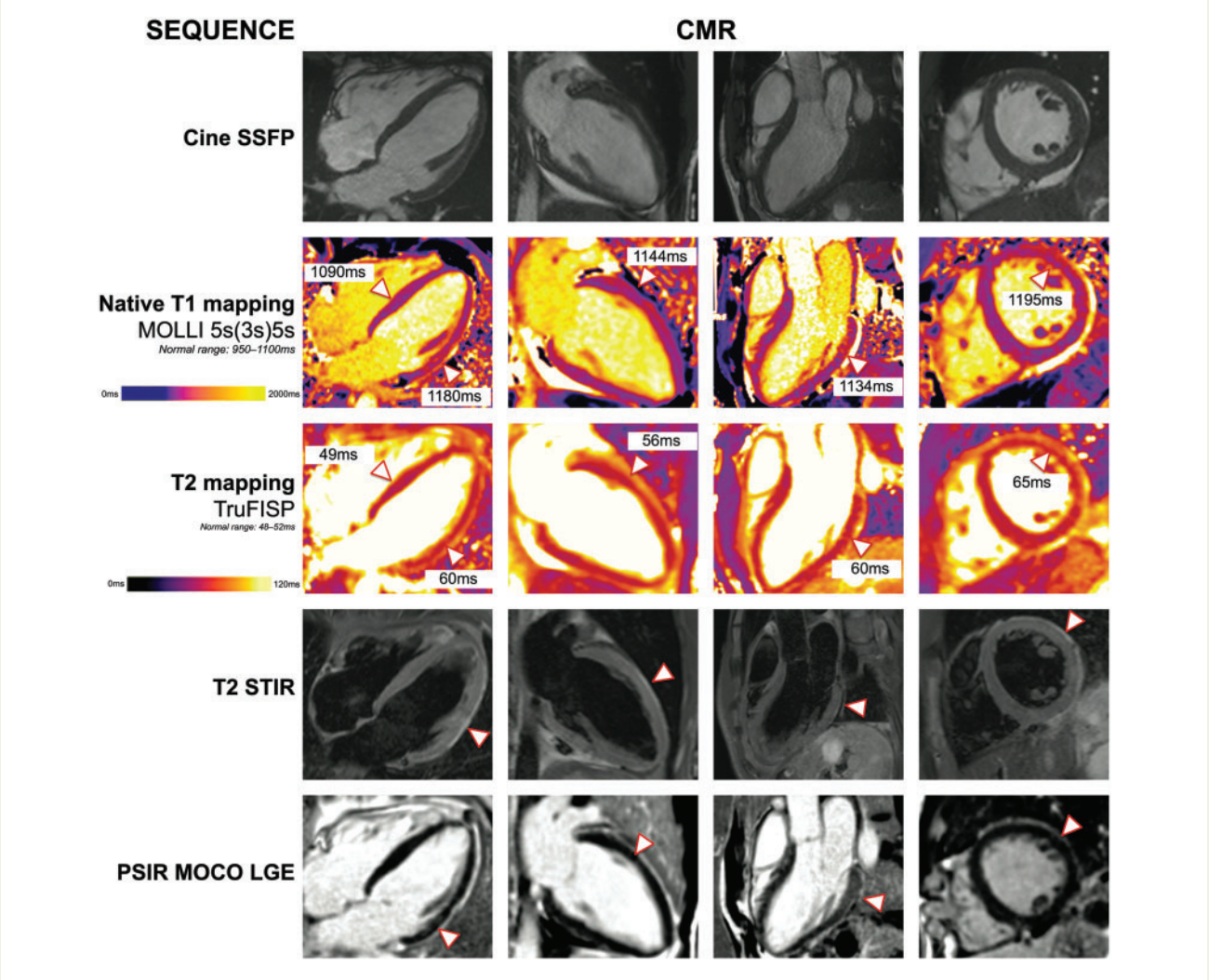


Figure 2 Multiparametric cardiovascular magnetic resonance imaging was in keeping with myocarditis. From left to right showing: four-chamber, two-chamber, three-chamber, and mid-left ventricular short-axis views. Cine stead-state free precession showed mildly increased left ventricular mass-index secondary to oedema, with normal biventricular systolic function, no regional wall motion abnormalities, and just trace pericardial effusion. Native T_1 mapping showed long T_1 in the lateral and mid-anterior wall and there was matching prolongation of the myocardial T_2 time on T_2 mapping and corresponding (albeit subtle) hyperintensity by short tau inversion recovery in these areas. Late gadolinium enhancement imaging showed low-volume 'fluffy' midwall myocardial fibrosis in the basal-to-mid lateral and mid-anterior wall matching the areas of abnormal T_1/T_2. CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; MOCO, motion-corrected; MOLLI, modified Look-Locker inversion recovery; PSIR, phase-sensitive inversion recovery; SSFP, stead-state free precession; STIR, short tau inversion recovery; TruFISP, true fast imaging with steady-state precession.

Electrocardiogram (ECG) on admission revealed sinus tachycardia (*Figure 1*) and the chest radiograph was unremarkable.

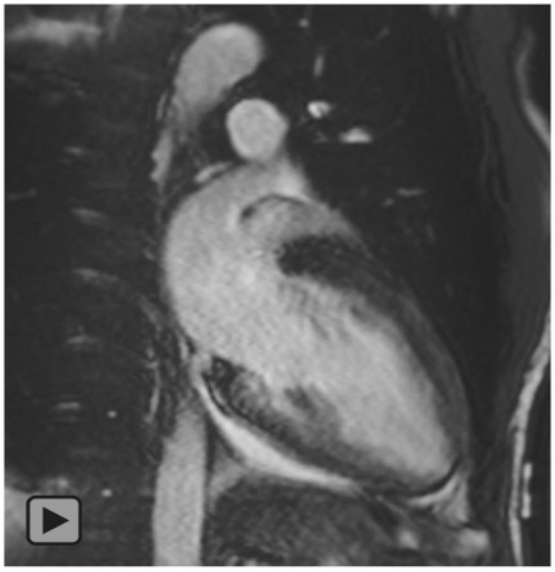
On account of the patient's raised troponin and high vasopressor requirements a bedside echocardiogram was performed on ICU. This demonstrated severe biventricular failure [left ventricular (LV) ejection fraction ~10%] without dilatation (*Video 1*).

Differential diagnosis

A diagnosis of fulminant myocarditis was made given the presence of severe biventricular dysfunction accompanied by evidence of myocardial necrosis (troponin rise). Furthermore, a diagnosis of HLH was felt to be likely on account of the dual lineage cytopaenia, fibrinogen consumption, raised ferritin and AST, and high fever in the context of overwhelming sepsis. The HScore[6] was 166, corresponding to a 48% predicted likelihood of HLH.

Management

The patient's condition continued to deteriorate on the ICU. His oxygenation worsened despite high flow nasal oxygen therapy and he was intubated to manage worsening type one respiratory failure. His antibiotics were changed to Clindamycin, Meropenem, Doxycycline, and Gentamicin. Continuous venovenous



Video 2 Cardiac magnetic resonance imaging obtained on Day 15 of admission demonstrates recovery of biventricular systolic function. Four-chamber cine then two-chamber cine.

haemofiltration (CVVHF) was commenced to manage oliguric acute kidney injury. His troponin continued to rise and peaked at 9338 ng/L. Infusions of Dobutamine and Levosimendan were commenced on account of worsening haemodynamic status and he was pre-emptively referred for consideration of mechanical circulatory support. No dysrhythmias were apparent on continuous ECG monitoring.

Given the presumptive diagnosis of HLH and patient's critical condition empirical treatment was commenced with intravenous Methylprednisolone 1 g daily and Anakinra 200 mg daily.

Over the next several days the patient's haemodynamic status improved markedly. Inotropic and ventilatory support were progressively weaned and he was extubated on the fourth day. Ventricular function as assessed by echocardiography improved. He began to pass urine and CVVHF was stopped. He was stepped down to the ward on the ninth day of admission and discharged another 9 days later.

Definitive investigations

Initial microbiological investigations were unremarkable. There was no growth in cultures of blood, urine, and sputum. Serology for human immunodeficiency virus, Hepatitis B, and Hepatitis C; and polymerase chain reaction (PCR) assays for Epstein–Barr virus, cytomegalovirus, herpes simplex virus, enterovirus, parvovirus, arbovirus, hantavirus, *Mycobacterium tuberculosis*, *Leptospirosis interrogans*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae* were negative.

PCR on blood at the national reference laboratory, reported 9 days after admission, detected *N. meningitidis* serotype W135. A bone marrow aspirate was reported as showing haemophagocytosis.

The patient underwent cardiovascular magnetic resonance (CMR) imaging at 1.5 Tesla (T) on the 15th day of admission (*Figure 2*). By this time, CMR showed normal biventricular systolic function but mildly increased LV mass (indexed to body surface area) attributed to swollen myocardial segments secondary to oedema. Indeed, parametric mapping confirmed prolonged native T1 times {up to 1195 ms by modified Look-Locker inversion recovery [MOLLI, *5 s(3s)3s*]} in the mid-anterior and lateral wall (normal reference range at our centre 950–1100ms). Matching this was prolonged T2 relaxation times (up to 65 ms by TruFISP T2 mapping, normal reference range 48–50ms) in the same segments. Additionally, there was 'fluffy' (soft) midwall (non-infarct pattern) late gadolinium enhancement (LGE) in the basal-to-mid lateral wall and mid-anterior wall. The CMR findings were in keeping with acute myocarditis.

Follow-up CMR 6 months later showed reduction in LV mass to normal values, low normal systolic function (ejection fraction 54%) and complete resolution of T1, T2, and LGE abnormalities. At this time the patient reported that he was completely asymptomatic and that he had not had any recurrence of his symptoms. His only medication was Ramipril. He remained well when reviewed in clinic 15 months after discharge, with normal exercise tolerance. He will continue routine follow-up in the cardiology clinic.

Discussion

The role of inflammation in cardiovascular disease has been understood for some time,[7] although it has received increasing prominence in recent years.[8] Individuals with elevated baseline CRP have been shown to have higher rates of major adverse cardiovascular events (MACE) than those with normal inflammatory markers,[9] while the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial[10] suggested that Canakinumab, a monoclonal antibody against IL-1β, is effective in reducing MACE in patients with previous myocardial infarction and an elevated CRP.

Laboratory studies have also demonstrated a role for inflammation in heart failure: van Tassell *et al.*[11] showed that administration of serum from patients with heart failure to healthy mice resulted in impaired LV function, and that this effect was reproduced by the administration of IL-1β and prevented by pre-treatment with Anakinra. Kumar *et al.*[12] replicated these results in rats.

There has been some success in translating these findings into the clinic. The Recently Decompensated Heart Failure Anakinra Response Trial (REDHART) trial[13] randomized patients with a recent decompensated heart failure admission and CRP >2 mg/L, to receive Anakinra or placebo. Those who received Anakinra for 12 weeks had an increase in peak oxygen consumption, although the trial was not powered to detect differences in rates of rehospitalization or death. The Tailored Immunosuppression in Inflammatory Cardiomyopathy (TIMIC) trial[14] randomized patients with chronic heart failure unresponsive to standard therapy and free of viral infection, to receive Azathioprine + Prednisolone, or placebo, in addition to standard heart failure therapy. Patients in the immunosuppression arm showed improvements in LV ejection fraction, reductions in LV volumes and improvement in New York Heart Association functional class, although hard outcomes such as MACE were not ascertained.

While inflammation clearly plays a role in the pathogenesis of acute myocarditis the role of therapies designed to suppress it remain poorly understood and consensus is lacking. One case report[3] describes the successful use of Anakinra in a man with perimyocarditis secondary to pharyngitis complicated by adult-onset Still's disease; the patient did not require haemodynamic support.

HLH is a hyperinflammatory syndrome characterized by the uncontrolled proliferation of cytotoxic T cells, natural killer cells, B cells, and macrophages, leading to a cytokine storm. This dysregulated immune response drives multiorgan dysfunction including bone marrow failure, coagulopathy, acute kidney and liver injury, and neurological impairment. HLH may arise from a genetically determined dysfunction of immune cells (previously termed 'primary' or 'familial' HLH) or in response to infection, malignancy, or an underlying autoimmune disease (previously termed 'secondary' or 'reactive' HLH, or 'macrophage activation syndrome').

In practice, differentiating between 'primary' and 'secondary' HLH has been shown to be clinically unhelpful, as both can be triggered by infections or other immune-activating events, and because gene mutations have been identified in individuals of any age and independent of family history. HLH genotyping is helpful because it can guide therapy in at-risk individuals. Mutations of the *PRF1* and *UNC13D* genes [Online Mendelian Inheritance in Man (OMIM) catalogue numbers 170280 and 608897] on chromosomes 10q22.1 and 17q25.1, which encode perforin 1 and Unc-13 Homolog D proteins, respectively, account for around 40–60% of genetically mediated cases. IL-1 plays a key role in the pathogenesis of HLH[4] and inhibition of IL-1 signalling with Anakinra has been associated with improved outcomes in patients with HLH, albeit in case series rather than randomized trials.[5,15]

In this case, the organism responsible for the patient's initial presentation with sepsis was only identified by PCR and the result was not available until the critical phase of his illness had resolved. Although multiple sets of blood cultures were taken at the time of admission this goes to reiterate the importance of taking samples for culture prior to the administration of antibiotics, whenever possible, and the value of molecular genetic testing in arriving at a precise diagnosis.

In the initial phases of the patient's illness we were faced with a critically unwell individual with multiorgan failure and no apparent aetiology. This case highlights the importance of echocardiography in the evaluation of refractory shock on the ICU, and the need to consider HLH in any patient with sepsis who fails to improve with or deteriorates in spite of treatment with antibiotics and supportive therapy.

In our patient, we hypothesize that the cytokine storm induced by meningococcal septicaemia triggered both HLH and fulminant myocarditis, with the immune overactivation and multiorgan dysfunction that are the hallmarks of the former condition, also exacerbating the latter. IL-1 likely played a key role in the pathogenesis of the patient's illness, explaining the very rapid and near complete recovery with Anakinra. Further research, in particular randomized controlled trials, are required to explore the role of IL-1 receptor antagonists in the treatment of fulminant myocarditis.

Conclusions

We describe the case of a young man who presented with non-specific infective symptoms and rapidly developed septic and cardiogenic shock. He was diagnosed with fulminant myocarditis and HLH, and was retrospectively found to have been infected with *N. meningitidis*. He was successfully treated with the IL-1 receptor antagonist Anakinra, following which he made a rapid and complete recovery.

Lead author biography

Ross J. Thomson studied medicine at New College, University of Oxford and is now a Specialist Registrar in Cardiology and NIHR Academic Clinical Fellow in London. His research is centred on the use of big data and real-world evidence to improve the diagnosis and management of cardiovascular disease. He sits on the finance committee of the British Cardiovascular Society and is the Lead Junior Editor at *European Heart Journal - Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

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