

Correspondence

Haemophagocytic lymphohistiocytosis after ChAdOx1 nCoV-19 vaccination

We report three cases of haemophagocytic lymphohistiocytosis (HLH) following the ChAdOx1 Astrazeneca vaccine. HLH is a rare but often fatal dysregulated hyper-immune response that clinically resembles sepsis.¹ It is classified as either familial, with known genetic defects in lymphocyte cytotoxicity identified (such as PRF1 or UNC13D mutations) or acquired/secondary HLH (sHLH). sHLH in adults is usually secondary to infection, malignancy or autoimmune disease, although HLH triggered by conventional vaccination such as influenza has been reported.²

The pathogenesis of sHLH is poorly understood but results from disruption to immune homeostasis, with aberrant activation of T cells, natural killer cells and macrophages leading to overproduction of inflammatory cytokines such as tumour necrosis factor (TNF)-alpha, TNF-gamma, interleukin (IL)-1, IL-2, IL-6 and haemophagocytosis.

Patients present with recurrent fever, cytopenia, liver dysfunction,

organomegaly, elevated ferritin and inflammatory markers and can rapidly progress to multiorgan failure. Early symptoms are often non-specific including wasting, fatigue, purpura, dyspnoea, diarrhoea, bleeding, rash, arthralgia and lymphadenopathy.³ The Histiocyte Society diagnostic criteria (HLH-2004) that were developed for paediatric-HLH diagnosis are commonly used in adult sHLH.

Patient 1, a male in his 60s with tablet-controlled type 2 diabetes mellitus was admitted to hospital 10 days after receiving the first dose of the ChAdOx1 vaccine. He presented with breathlessness, fevers and myalgia with onset of symptoms 5 days postvaccination. He was commenced on broad spectrum antibiotics for presumed infection. CT pulmonary angiography excluded pulmonary emboli but highlighted bilateral pleural effusions. Echocardiogram showed normal biventricular systolic function. An elevated ferritin raised the possibility of HLH that was subsequently confirmed on further investigation.

Despite HLH treatment, he deteriorated with worsening cardiac and renal failure. A repeat transthoracic echocardiogram showed severe left ventricular (LV) systolic dysfunction. He was transferred to intensive care for management of cardiac failure with vasopressors and

continuous veno-venous haemofiltration (CVVH). Second-line therapy was commenced leading to a rapid biochemical improvement.

Patient 2, a female in her 70s with stable JAK2-mutation positive essential thrombocythaemia, breast cancer in remission and a history of bee sting anaphylaxis developed night sweats, breathlessness and myalgia 7 days after receiving the first dose of ChAdOx1 vaccine. She was reviewed after a chest X-ray demonstrated a right upper zone opacity. CT showed bilateral patchy infiltrates consistent with an acute pneumonitis. She was empirically treated with oral antibiotics but was later admitted to hospital due to persistent fever and switched to intravenous antibiotics. Transthoracic echocardiogram was normal. Fevers settled, and the patient was discharged. She was readmitted with progressive fevers, breathlessness, cough, weight loss and general malaise and an elevated serum ferritin. Repeat cross-sectional imaging showed progressive bilateral ground-glass opacities.

HLH was confirmed on further investigation. Repeat echocardiogram showed significant deterioration in LV function. She developed atrial fibrillation with haemodynamic compromise and a spontaneous pneumothorax requiring admission to the intensive care unit for vasopressors and CVVH and a chest drain. Sadly, despite treatment, she deteriorated and spontaneously developed a ruptured oesophagus; she died the following day.

Patient 3, a male in his 30s with ankylosing spondylitis became unwell 8 days after receiving the first dose of ChAdOx1 vaccine with fever, diarrhoea, sore throat and pruritic rash. He was admitted to hospital 15 days later with worsening symptoms and breathlessness. CT demonstrated bilateral lung consolidation, pleural effusions, a pericardial effusion of 1.5 cm diameter and mild splenomegaly. Echocardiogram showed mild left ventricular systolic dysfunction. Despite antibiotic therapy, the patient continued to deteriorate with persistent fever and hypoxia. Repeat echocardiogram showed deterioration in LV systolic function. A positron emission tomography (PET) CT scan showed intense bone marrow uptake and hypersplenism (see figure 1). Further investigations confirmed HLH. The patient responded well to first-line therapy.

All three patients presented with elevated inflammatory markers, with subsequent evidence of HLH highlighted by elevated ferritin, cytopenias, hypofibrinogenaemia, hypertriglyceridaemia, elevated liver enzymes and high levels of soluble CD25

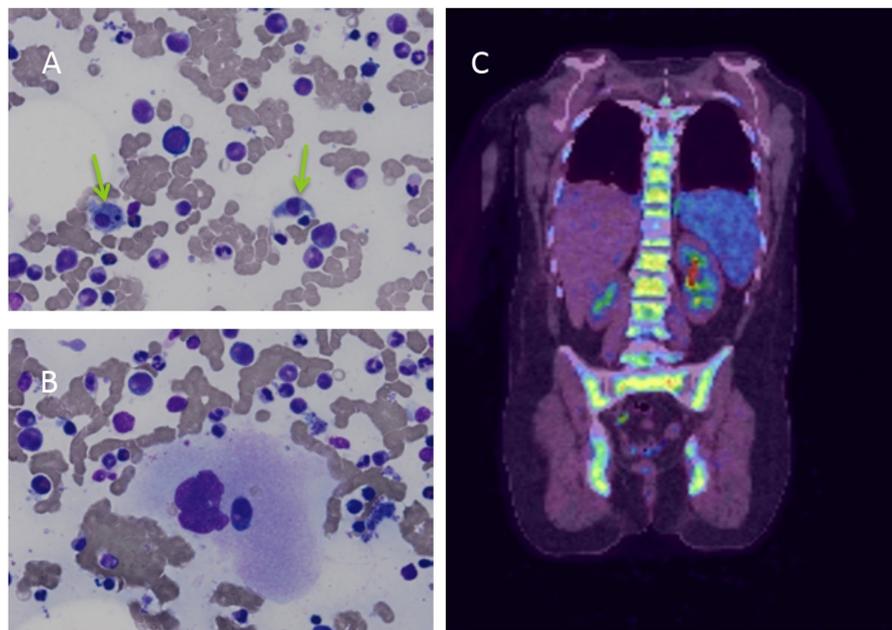


Figure 1 Diagnosis of haemophagocytosis. (A) Bone marrow aspirate ($\times 50$) from case 1 showing two histiocytes (arrows) phagocytosing an erythrocyte and some platelets. (B) Bone marrow aspirate ($\times 100$) from case 1 showing a macrophage phagocytosing an erythrocyte. (C) PET-CT from case 3 showing intense FDG uptake in bone marrow and to lesser extent spleen. PET-CT can be a useful tool to exclude secondary causes of HLH but also identify sites of haemophagocytosis. HLH, haemophagocytic lymphohistiocytosis; PET, positron emission tomography.

Table 1 Diagnosis of HLH; diagnostic criteria and laboratory results of cases

(A) The diagnosis of HLH can be established if criterion 1 or 2 is fulfilled			
A molecular diagnosis consistent with HLH			
Diagnostic criteria for HLH fulfilled (5 of 8 criteria below)			
Fever			
Splenomegaly			
Cytopenias (affecting >2 of 3 lineages in peripheral blood)			
Haemoglobin <9.0g/dL, platelets <100×10 ⁹ /L, neutrophils <100×10 ⁹ /L			
Hypertriglyceridaemia and/or hypofibrinogenaemia			
Fasting triglycerides ≥3.0 mmol/L, fibrinogen <1.5g/L			
Haemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy			
Low or no natural killer (NK) cell activity			
Ferritin ≥500 µg/L			
sCD25 (soluble interleukin (IL)-2 receptor) ≥2400 U/mL			
(B) Clinical and laboratory features	Case 1	Case 2	Case 3
Time to onset symptoms post vaccination (days)	5	7	8
Temperature (38.4–39.4°C)	39.3	39.2	41.2
Organomegaly	Yes (hepatomegaly)	No	Yes (splenomegaly)
Haemoglobin (Normal range (NR) 120–150g/L)	10.1	11.9	10.5
Platelets (NR 150–400×10 ⁹ /L)	54	69	319
Ferritin (NR 15–400 µg/L)	159076	5529	58255
Lactate dehydrogenase (LDH) (NR 90–275 iU/L)	536	1178	541
Triglyceride (NR 0.5–2.3 mmol/L)	6.3	2	2.7
Fibrinogen (NR 2.12–4.88 g/L)	0.7	0.94	4.17
Alanine aminotransferase (ALT) (NR 0–35 iu/L)	132		47
Troponin (NR <14 ng/L)	299	312	42
Haemophagocytosis on bone marrow biopsy	Yes	Yes	Yes*
sCD25 (0–2500 pg/mL)	4833	9232	3575*
HScore for HLH (% probability)	259 (>99)	220 (96)	219 (96)

(A) HLH-2004 diagnostic. (B) Laboratory results of cases 1–3 at time of diagnosis.

*In case 3, undertaken after 3 days of methylprednisolone.

HLH, haemophagocytic lymphohistiocytosis.

the finding that the IL-6 inhibitor tocilizumab improves outcomes in patients hospitalised with COVID-19.⁶ Furthermore, there are some reports that anakinra can improve outcomes in this patient group and also COVID-19 induced sHLH.⁷

The ChAdOx1 vaccine consists of a replication-deficient chimpanzee-derived adenovirus vector containing the SARS-CoV2 surface glycoprotein antigen (spike protein). It clearly causes dramatic proinflammatory responses in some individuals, previously highlighted by the discovery of pathologic anti-PF4 antibodies in patients presenting with thrombocytopenia and thrombosis after the first vaccine dose.⁸ Further investigation is warranted to understand underlying mechanisms and which component of the vaccine may be implicated: the adenovirus vector or COVID-19 spike protein.

We report here the first described cases of vaccine induced HLH secondary to the ChAdOx1 vaccine. Other causes of sHLH were excluded, and we therefore propose that the likely trigger was the recent vaccination. All patients developed moderate to severe cardiac dysfunction, an uncommon finding in other case series of sHLH. Physicians should be aware of HLH as early recognition and initiation of anakinra may prevent irreversible organ damage and death. We recommend careful consideration of the timing and options for alternative SARS-CoV-2 vaccines in patients predisposed to HLH such as in the post allogeneic or CAR-T cell setting.

(see table 1). Other secondary causes of HLH were excluded by cross-sectional imaging, extensive negative infection screening including serial COVID-19 testing and negative autoimmune panels.

Once the diagnosis of HLH was considered and confirmed, all three patients were treated with high-dose methylprednisolone 500 mg intravenously daily for 3 days, followed by prednisolone 60 mg (or equivalent) daily. Patients 1 and 2 required second-line immune-suppression with intravenous immunoglobulin and the IL-1 receptor antagonist anakinra, 100 mg subcutaneously daily (later increased to 200 mg due to deterioration and requirement for intensive care support) with a good biochemical response (see figure 2). Sadly, patient 2 developed catastrophic complications with oesophageal rupture, possibly related to gastrointestinal involvement with sHLH, leading to death.

HLH has been reported as a consequence of SARS-CoV-2 infection, and there is some evidence that sHLH is underdiagnosed in severe COVID-19

illness.⁴ Both lead to a hyperinflammatory syndrome and a severe cytokine storm with elevated ferritin levels being associated with poor outcomes in COVID-19 and sHLH.⁵ This underpins

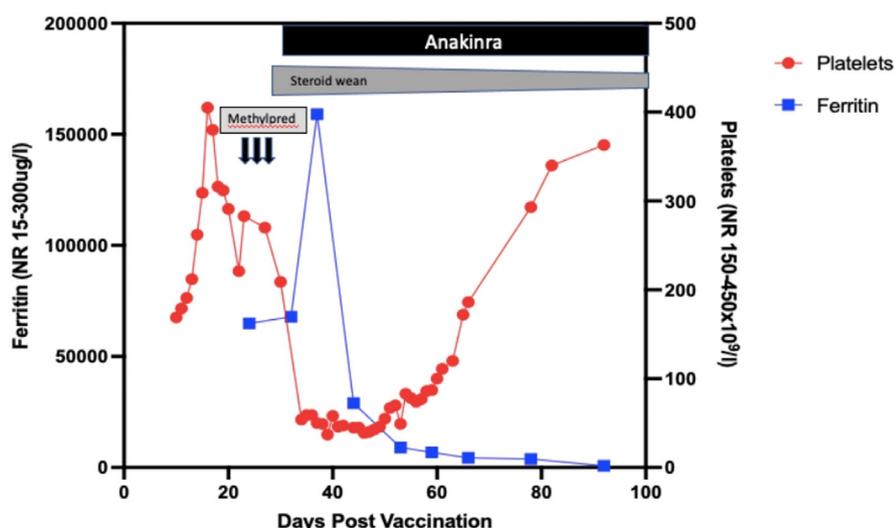


Figure 2 Timeline of progression postvaccination for patient 1 with serum ferritin and platelet count and introduction of therapy indicated. NR, normal range.

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