Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

clinical findings in these three patients were clearly indicative of this condition.

Although we cannot exclude the possibility that the onset of vasculitis following vaccination was coincidental, striking similarities between these three patients argue for pathogenic causality. Specifically, vasculitis developed in healthy individuals with no personal or family history of autoimmunity; clinical manifestations were similar and characterised by widespread cutaneous vasculitis with no visceral involvement; and there was a temporal association between vaccination and the development of clinical manifestations, with no other intercurrent inciting events. All patients underwent serologic testing for SARS-CoV-2 infection before vaccination and tested negative, indicating no previous primary infection: hence, vasculitis might have been triggered by maladaptive individual immune responses to a component of the vaccine.

The ChAdOx1 nCoV-19 vaccine contains recombinant adenoviral vectors encoding the spike protein of SARS-CoV-2, stabilisers, and immune adjuvants. It is possible that molecular mimicry might develop between the peptides that are expressed in the viral spike protein and in the host endothelial cells, particularly following non-specific adjuvant effects. Vasculitis can develop during COVID-19 because of direct endothelial damage,[3-5] and coagulation disorders can develop following vaccination with ChAdOx1 nCoV-19 because of platelet-activating antibodies against platelet factor 4 (PF4).[6] Thereby, we speculate that maladaptive immune activation induced by vaccination affects the endothelial layer or the coagulation cascade, ultimately inducing vasculitis in predisposed individuals.

SARS-CoV-2 infection has resulted in more than 4 million deaths worldwide, often due to excessive or aberrant host immune responses.[7] The benefits of vaccination outweigh the risks,[8] yet vaccination of millions of individuals is unavoidably complicated by sparse immune-mediated adverse events, since proinflammatory stimulation can expose individual predisposition to the development of maladaptive immune responses.[9-11]

GC led the study and wrote the report. GC, GDL, SC, RP, FC, and LD took clinical care of patients, obtained data, and contributed to drafting the manuscript. NR conducted histology evaluations. Written informed consent for publication was obtained from the patients. We declare no competing interests.

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Haemophagocytic lymphohistiocytosis secondary to COVID-19: a case series

Published **Online** August 16, 2021 https://doi.org/10.1016/S2665-9913(21)00248-4

A pathological, dysregulated immune response (ie, hyperinflammation) is a recognised complication of COVID-19.[1] The prototypical hyperinflammatory syndrome secondary to infection is secondary haemophagocytic lymphohistiocytosis (sHLH), but the dominant hyperinflammatory phenotype in people

with severe COVID-19-associated pneumonia is not that of sHLH and is poorly understood.[1,2] The COVID-19 hyperinflammation phenotype is associated with increased concentrations of inflammatory markers, increased risk of mortality, and subsequent development of immunothrombosis.[2,3]

A small subgroup of people with COVID-19, however, do develop classic sHLH,[4] in which pathological immune dysfunction and unchecked production of inflammatory cytokines result in multiorgan failure. Risk factors for sHLH include infection, such as COVID-19, but also genetic risk factors, haematological malignancy, autoimmune or autoinflammatory disease, severe burns, and oncological treatments.[5] Identifying people in whom COVID-19 has triggered sHLH is important because sHLH has a high mortality, and early intervention with established treatments can reduce death and the need for toxic therapy.[5,6]

Diagnosis of sHLH is a challenge. Evidence-based scoring systems include the H-score and haemophagocytic lymphohistiocytosis (HLH)-2004 criteria. Both have limitations, however. The H-score is not validated in critical care, and in the first wave of the pandemic, with health systems under huge pressure, some of the required tests were simply not feasible (eg, imaging for organomegaly and bone marrow biopsy). HLH-2004, although widely used in adults, is validated only in children. In practice, clinicians often use a combination of scoring systems and clinical judgement, with input from specialist HLH multidisciplinary teams.[7]

Treatment for patients with sHLH is with immune modulation, but a robust evidence base does not exist. Treatments include glucocorticoids, intravenous immunoglobulin, ciclosporin, etoposide, and the recombinant interleukin-1 receptor antagonist, anakinra, which has a good safety profile in infection.[8] Unlicensed use of anakinra has been associated with reduced mortality in patients with sHLH.[9] Anakinra has therefore been adopted as part of standard of care for management of patients with sHLH in some UK

	Sex	Age, years	Notable comorbidities	Time from admission to secondary haemophagocytic lymphohistiocytosis diagnosis, days	Peak ferritin, µg/L	Mechanical ventilation	Inotropic support	Renal replacement therapy	Other treatments received	Final patient outcome (days to death or discharge)
Patient 1	Male	40	Acute lymphoblastic leukaemia	28	76 225	Yes	No	No	Piperacillin and tazobactam preparation, meropenem, and liposomal amphotericin B	Died (74)
Patient 2	Male	28	Recurrent pneumonias	6	3164	Yes	Yes	No	Cefuroxime	Died (7)
Patient 3	Male	36	Acute lymphoblastic leukaemia	12	17 085	No	No	No	Meropenem, liposomal amphotericin B, and filgrastim	Discharged (31)
Patient 4	Male	36	No medical history	1	5736	Yes	Yes	No	Potassium clavulanate and amoxicillin preparation	Discharged (16)
Patient 5	Female	60	Systemic lupus erythematosus	3	12 402	Yes	Yes	Yes	Glucocorticoids (ie, for systemic lupus erythematosus)	Died (42)
Patient 6	Male	56	Asthma	3	9245	Yes	Yes	No	Potassium clavulanate and amoxicillin preparation and meropenem	Discharged (43)
Patient 7	Male	63	Type 2 diabetes and atrial fibrillation	0	17 790	Yes	Yes	No	Potassium clavulanate and amoxicillin preparation and piperacillin and tazobactam preparation	Discharged (11)
Patient 8	Male	54	Asthma	0	19 078	Yes	Yes	Yes	Glucocorticoids, potassium clavulanate and amoxicillin preparation, piperacillin and tazobactam preparation, and meropenem	Died (32)
Patient 9	Male	52	Previous deep vein thrombosis	1	12 607	Yes	Yes	Yes	Piperacillin and tazobactam preparation, clarithromycin, meropenem, vancomycin, and ciprofloxacin	Discharged (96)
Patient 10	Female	22	Sickle cell trait	9	45 864	No	Yes	No	Piperacillin and tazobactam preparation, ciprofloxacin, clindamycin, metronidazole, meropenem, linezolid, ceftazidime, and fluconazole	Discharged (40)

Table: **Summary of patient demographics and treatments received that were not specific to secondary haemophagocytic lymphohistiocytosis by patient**

National Health Service trusts under locally agreed guidelines.

Here, we present a series of patients with HLH secondary to infection with SARS-CoV-2. We also discuss the challenges of diagnosis and treatment of sHLH during a pandemic.

All patients with COVID-19 that met agreed criteria for sHLH (ie, on the basis of clinical picture and H-score) and were admitted to University College Hospital (London, UK), Sheffield Teaching Hospitals National Health Service Foundation Trust (Sheffield, UK), or Luton and Dunstable Hospital (Luton, UK) between Feb 1 and June 15, 2020, were reviewed. Diagnosis of COVID-19 was confirmed with SARS-CoV-2 PCR on nasopharyngeal swab or clinical diagnosis was made on review by an infectious diseases' consultant at a tertiary centre. Patients were included in this evaluation if informed written consent was obtained. The project was registered with local clinical governance departments. Ethical approval was not required as this analysis was approved under local service evaluation permissions.

Data that were available from health records were collated and used to calculate the H-score, as defined according to Fardet and colleagues but modified to omit assessment of organomegaly and bone marrow cytology.[10] Thus, the modified possible total score was 264, with the median score that was suggestive of sHLH of 132; following the model from Kyriazopoulou and colleagues.[1,11]

See Online for appendix

We present data from ten patients with COVID-19-induced sHLH (see appendix pp 2–5 for two detailed case vignettes). The median patient age was 46 years (range 22–63 years) and 90% (nine) of patients were male. All ten patients required admission to intensive care.

Three of ten patients had another underlying diagnosis that might have contributed to the development of sHLH: two patients had acute lymphoblastic leukaemia and one patient had poorly controlled systemic lupus erythematosus (table). Two of ten patients were healthcare staff (one consultant surgeon and one medical student).

The median H-Score at diagnosis was 164 (IQR 125–184), which was reduced to 84 (63–99) by day 14 after treatment initiation in survivors, with a median change of –72 (–50 to –83). The median ferritin concentration at diagnosis was 9576 µg/L (8058–12090 µg/L), which was reduced to 3034 µg/L (1904–3895 µg/L) by day 14 after treatment initiation, with a median change of –6925 µg/L (–3969 to –10726); appendix pp 6, 8). The median peak ferritin was 14 846 µg/L (10 034–18 756). All patients had cytopenia of at least one cell type, eight patients had increased triglyceride concentration, and nine patients had increased concentration of ALT.

All patients were treated with anakinra, as per local guidelines. Nine of ten patients received intravenous anakinra and one received subcutaneous anakinra. The initial daily intravenous dose ranged from 140 mg to 600 mg. In addition to anakinra, one patient was also treated with intravenous immunoglobulin; one patient with intravenous immunoglobulin and methylprednisolone; and one patient with intravenous immunoglobulin, methylprednisolone, and ciclosporin (appendix p 7).

Four (40%) of ten patients died; two patients due to worsening multiorgan failure with circulatory collapse, one patient due to worsening respiratory failure, and one due to resistant autoimmune myocarditis secondary to poorly controlled systemic lupus erythematosus. One patient required readmission for further treatment (see appendix pp 2–3 for case vignette). At the time of analysis, all surviving patients had been successfully discharged.

Here, we show that sHLH complicates COVID-19 in a small number of patients and that confident diagnosis is possible even in a health system under pressure. The mortality of our patients was 40% (four of ten patients); compared with the 39% (4287 of 10 904) mortality that was seen in the first wave of patients with COVID-19 who were admitted to intensive care in the UK and 68% (48 of 71) mortality seen in a previous series of patients with sHLH.[5,12]

At the time that our patients were treated (ie, before the benefit of dexamethasone was shown), concern existed about the use of corticosteroids in patients with COVID-19-induced acute respiratory distress syndrome, so anakinra was used in preference. Dosing of anakinra was determined by clinical experience and the literature that was available at the time.[9] Our findings are consistent with previous use of anakinra in patients with sHLH, specifically: a decrease in ferritin and temperature, mortality within the range of previous work, and increased mortality in patients with underlying haematological disease.[5,6]

Although we present a small number of patients, there was a clear preponderance for men to develop sHLH in this cohort. This difference might in part reflect the increased proportion of men requiring admission to intensive care secondary for COVID-19 during this time (70% men *vs* 30% women). No patients had severe adverse effects that were obviously attributable to anakinra.

Successful management of patients with sHLH relies on an experienced multidisciplinary team approach. The UK based group, Hyperinflammation and HLH Across Speciality Collaboration, is one such example and includes specialists in rheumatology, haematology, critical care, infectious diseases, virology, neurology, nephrology, and cardiology.

The complex, dynamic, and non-specific nature of sHLH means that it cannot easily be summarised with numerical parameters, and a binary diagnostic approach is not always possible. It is plausible that a proportion of patients who are critically ill (with COVID-19 or other diseases) and do not respond to conventional treatments have developed undiagnosed sHLH. The important clinical questions in such a scenario might be whether the person is suffering from systemic hyperinflammation and whether the benefits of immunomodulation outweigh the risks. If the answers to both these questions are yes, then early, experienced multidisciplinary consult and treatment initiation should be considered.

The COVID-19 pandemic has taught the medical community many things, not least the fact that multicentre, randomised controlled trials of immune modulation are feasible in patients who are critically ill. Perhaps this knowledge and infrastructure can be harnessed for patients with sHLH.

We declare no competing interests. JJM and VQ shared last authorship. LF, NL, JJM, RT, and VQ had full access to all the data in the study and had final responsibility for the decision to submit for publication. There was no funding source for this study.

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Inflammatory myositis after ChAdOx1 vaccination

Published **Online**
September 23, 2021
https://doi.org/10.1016/S2665-9913(21)00312-X

Most adverse events after immunisation with adenoviral vector vaccines—such as ChAdOx1 nCoV-19 (Oxford–AstraZeneca) and Ad26.COV2.S (Janssen)—are mild; however, rare life-threatening adverse events such as thrombosis with thrombocytopenia syndrome or Guillain-Barré syndrome have been reported.[1,2] Over a 6-month period comprising January to June, 2021, we encountered three cases of post-vaccination myositis at our hospital.

A 74-year-old man presented with a 3-week history of intermittent low-grade fever and polyarthralgia. These symptoms started 48 h after his first dose of ChAdOx1 nCoV-19 vaccination. The patient was febrile (38·5°C), tachycardic, and had tenderness in both calf muscles. Elevated inflammatory parameters were noted (appendix). On day 26, ^{18}FDG-PET-CT showed a tree-root-like uptake pattern in the lower limbs suggestive of

See **Online** for appendix