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.

with less than four positive samples in that week. They show shifts in the proportion of higher CT value tests, defined here as CT value >30, changing with community prevalence (Table 1). An increased proportion of high CT value tests were seen as case numbers declined, and the opposite was observed as numbers increased again in March. Graphical representation of the data, generated using R with *ggridges* package,[3] shows the changing distribution of CT values and in some instances the emergence of a bimodal curve reflecting probable distinct cohorts of past and acute infection (Fig. 1).

Although these tests are primarily designed to be qualitative and not quantitative, the use of CT values to assist with distinguishing acute from historical infection is widely accepted. Individual CT values obtained from different testing platforms may not be directly comparable, but large scale population data should smooth errors allowing valid interpretation of overall trends. These data suggest that analysis of CT values across a population may afford useful information that may be of assistance to public health efforts and add refinement to epidemiological models to predict community transmission. Further study should be considered.

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Severe autoimmune haemolytic anaemia following SARS-CoV-2 vaccination in patients with treatment naïve B-cell neoplasms: a case series

To the Editor,
A concerted global health initiative has led to the development of multiple effective vaccinations to help combat the SARS-CoV-2 (COVID-19) pandemic. While the safety of these vaccines has been demonstrated in large, randomised studies, the incidence of rare complications, particularly in specific health subgroups such as haematological malignancies, is important to establish.

Autoimmune haemolytic anaemia (AIHA), a condition typified by antibody-mediated destruction of erythrocytes, has been reported in the setting of COVID-19.[1–3] B-cell neoplasms are also a known driver of AIHA. We report four patients with a pre-existing or new concurrent diagnosis of B-cell neoplasms, who were diagnosed with first presentation severe AIHA following COVID-19 vaccination at our tertiary centres. We highlight that patients with B-cell malignancies may be an at-risk group for this rare immune complication following COVID-19 vaccination, and discuss management strategies.

Case 1 was a 76-year-old male with a history of untreated chronic lymphocytic leukaemia (CLL) RAI stage-0, presenting with malaise, lethargy and abdominal pain 4 days following his first dose of the ChAdOx1nCoV-19 vaccine. His baseline bloods, prior to vaccination, demonstrated a haemoglobin 133 g/L, white cell count (WCC) 60×10^9, lymphocyte count 32×10^9 and bilirubin of 7 mcmol/L (0–20). On presentation his haemoglobin had fallen to 59 g/L (Table 1), with spherocytosis on blood film, and a reticulocytosis of 11.6%. A marked lymphocytosis was observed, with WCC 239×10^9/L and a lymphocyte count 220×10^9/L. SARS-CoV-2 polymerase chain reaction (PCR) was negative. There was biochemical evidence of haemolysis with bilirubin of 97 mcmol/L, haptoglobin <0.01 g/L (0.36–1.95) and lactate dehydrogenase (LDH) 835 U/L (120–250). Direct antiglobulin testing (DAT) was positive for C3d and negative for IgG, in contrast to his previously negative DAT in 2014. He was diagnosed with AIHA and commenced on prednisolone 1 mg/kg, warmed supportive red blood cell (RBC) transfusions to account for potential cold AIHA, and a single infusion of intravenous immunoglobulin (IVIg, 1 g/kg). CLL therapy was considered given the patient's progressive lymphocytosis and aggressive AIHA, however after 4 days his haemoglobin stabilised without transfusion. Prednisolone was slowly weaned, and one month post-admission, his WCC and lymphocyte count had returned to their pre-vaccination baseline. He received the BNT162b2 vaccine (Pfizer) for subsequent doses, with a mild relapse of haemolysis following the second, but not third dose, which responded to prednisolone. However, 6 months later he had an 'unprovoked' relapse of AIHA which responded to prednisolone and IVIg.

Case 2 was a 49-year-old male presenting 4 days following his second dose of the BNT162b2 COVID-19 vaccine with worsening exertional dyspnoea and central chest discomfort on a background of stable CLL. This was preceded with dark coloured urine, which in retrospect he had also noticed following the first vaccine. His baseline bloods included a haemoglobin 156 g/L, WCC 13.7×10^9, and lymphocyte count 10.0×10^9. His presenting investigations demonstrated a haemoglobin of 39 g/L, WCC 35.7×10^9/L with lymphocytosis of 27.8×10^9/L, and reticulocytes were 25.1% (Table 1). SARS-CoV-2 PCR was negative. A blood film showed moderate polychromasia, frequent spherocytes and presence of nucleated RBCs (8/100 WCC). A haemolysis screen demonstrated a raised bilirubin of 87 mcmol/L, haptoglobin of <0.01 g/L, and raised LDH of 953 U/L, with DAT positive for IgG and C3d (no prior DAT for comparison). The patient was commenced on prednisolone 1 mg/kg and supportive RBC transfusions. By day 5, his haemoglobin

Table 1 Clinical overview and management of patients with autoimmune haemolytic anaemia following COVID-19 vaccinations

Case no.	Age (years)	Sex	Underlying malignancy	Vaccine received	Time from vaccination to admission	Hb on presentation (g/L)	Bilirubin on presentation (mcmol/L)	LDH on presentation (U/L)	DAT	Management	Hb response (g/L)
1	76	M	Chronic lymphocytic leukaemia	ChAdOx1nCoV-19	4 days	59	97	835	IgG (−); C3d (+)	First line: - RBC transfusion - Prednisolone 1 mg/Kg - IVIg Second line at relapse: - RBC transfusion - Prednisolone 1 mg/Kg - IVIg	112
2	49	M	Chronic lymphocytic leukaemia	BNT162b2	4 days	39	87	685	IgG (+); C3d (+)	First line: - RBC transfusion - Prednisolone 1 mg/Kg	123
3	83	F	Splenic marginal zone lymphoma	ChAdOx1nCoV-19	30 days	57	50	2124	IgG (+); C3d (+)	First line: - RBC transfusion - IVIg - Prednisolone 1 mg/kg Second line at relapse: - Chemo-immunotherapy (R-CVP)	117
4	64	M	Chronic lymphocytic leukaemia	ChAdOx1nCoV-19	37 days	55	39	488	IgG (+); C3d (−)	First line: - RBC transfusion - Prednisolone 1 mg/kg Second line at relapse: - Rituximab ×4 doses	123

DAT, direct antiglobulin testing; F, female; Hb, haemoglobin; IVIg, intravenous immunoglobulin; LDH, lactate dehydrogenase; M, male; RBC, red blood cell; R-CVP, rituximab cyclophosphamide vincristine prednisolone.

stabilised and incremented without transfusions. As his prednisolone was weaned in the community, his haemoglobin normalised with WCC returning to pre-vaccination baseline.

Case 3 was an 83-year-old female with no known history of haematological malignancy, presenting with progressive fatigue, malaise and anorexia following her first dose of the ChAdOx1nCoV-19 vaccine one month prior. Her initial blood tests showed a haemoglobin 57 g/L, WCC 5.6×10^9 with a normal differential, and platelets of 204×10^9/L (Table 1). She had a reticulocytosis of 243×10^9/L, with occasional nucleated RBCs on blood film, haptoglobin of <0.10, LDH of 2124 U/L and bilirubin of 50 mcmol/L. SARS-CoV-2 PCR was negative. A DAT was positive for IgG and C3d (no prior DAT for comparison). She was managed with supportive RBC transfusions and received two doses of IVIg (1 g/kg), with prednisolone delayed pending a bone marrow aspirate and trephine (BMAT) sample. The BMAT and flow cytometry revealed marrow involvement with a low-grade B-cell lymphoma, most consistent with splenic marginal zone lymphoma (SMZL). Splenomegaly measuring 17.7 cm was seen on computed tomography (CT) of the abdomen and pelvis. The patient was commenced on prednisolone 1 mg/kg, discharging 4 days later with improvement of her haemolysis. On discharge, her bilirubin normalised, LDH reduced to 957 U/L, and her haemoglobin was 80 g/L. Prednisolone was weaned over weeks and her haemoglobin stabilised at 117 g/L, haptoglobin of <0.10 g/L with a normal bilirubin. She subsequently had a relapse of haemolysis on weaning of prednisolone and required commencement of R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone) chemo-immunotherapy regimen.

Case 4 was a 64-year-old male who was referred with ultrasound findings demonstrating a right lower limb deep vein thrombosis approximately 37 days following his ChAdOx1nCoV-19 vaccine without a background of a known haematological malignancy. His presenting investigations demonstrated a haemoglobin 55 g/L, reticulocyte count of 14.35%, and a raised WCC 45×10^9 with lymphocyte count 35×10^9. SARS-CoV-2 PCR was negative. AIHA was further evidenced by a haptoglobin of <0.08 g/L, bilirubin of 39 mcmol/L, LDH of 488 U/L, and DAT positive for IgG (Table 1) (no prior DAT for comparison). CT pulmonary angiogram demonstrated multiple bilateral subsegmental pulmonary embolism without right heart strain, which was initially managed with therapeutic enoxaparin before transitioning to apixaban on discharge. CT of the abdomen and pelvis showed cervical lymphadenopathy and splenomegaly measuring 14 cm. Flow cytometry of the peripheral blood showed an abnormal population of lymphocytes with antigen expression consistent with CLL. He was diagnosed with new CLL and AIHA. The patient was commenced on prednisolone 1 mg/kg, discharging after 12 days with a haemoglobin of 85 g/L, which further incremented to 96 g/L in the community. On weaning of prednisolone, he had a flare of haemolysis necessitating escalation of prednisolone, IVIg and four doses of rituximab with improvement of his haemoglobin to 106 g/L with slowly improving haemolytic markers.

B-cell lymphoproliferative disorders are associated with defects in humoral and cellular immunity that results in both immunosuppression and immune dysregulation[4] such as AIHA. Patients with B-cell malignancies appear to have a greater risk of significant morbidity and mortality due to COVID-19.[5] Preventative strategies, such as vaccination, are particularly important for this vulnerable patient group.

Numerous case reports/series have documented an association between COVID-19 infection and incidence of warm and cold AIHA.[6] In a systematic review including 50 patients with COVID-19 complicated by AIHA, five patients (10%) were reported to have CLL and a further two patients (4%) had marginal zone lymphoma.[6] Similarly, Lazarian *et al.* reported seven patients who developed AIHA in the setting of COVID-19, four of whom had a B-cell malignancy.[1] Given the low prevalence of these conditions, this suggests that patients with B-cell neoplasms are at an increased risk of this autoimmune complication.

In the systematic review by Jacobs and Booth, four case reports of AIHA following either Pfizer or Moderna mRNA COVID-19 vaccines were identified.[6] We have identified another two isolated case reports of AIHA following the Moderna mRNA vaccine.[7,8] To our knowledge, this case series is the first documentation of this complication in patients with B-cell haematological malignancies and following the ChAdOx1nCoV-19 adenoviral vector vaccine. In contrast to the limited available literature, we have only identified this complication in patients with concurrent or pre-existing B-cell neoplasms and based on our experience would suggest that this population is at an increased risk of this rare complication, similarly to what appears to be the case following COVID-19 infection.

Angileri *et al.* proposed molecular mimicry as the pathogenic driver of AIHA in patients with COVID-19 due to the similarity between Ankyrin 1 (ANK-1), a protein found on the membrane of erythrocytes and the viral spike protein, with 100% homology in a putative immunogenic-antigenic epitope (amino acids LLLQY).[3] As both the BNT162b2 and mRNA-127 mRNA vaccines encode the viral spike protein, and the ChAdOx1nCoV-19 vaccination incorporates the viral spike protein to induce the required immune response, we hypothesise that this mechanism is potentially responsible for the development of AIHA in this setting.[9]

Importantly, whilst all patients presented with severe anaemia requiring inpatient admission and initial transfusion support, all patients responded to first line therapy with prednisolone +/− IVIg. The first two cases with known CLL developed a concurrent exacerbation of peripheral lymphocytosis (6-fold and 2.5-fold, respectively), which resolved over a similar trajectory as their AIHA. A similar exacerbation of lymphocytosis has also been reported in multiple patients with CLL who have been infected with COVID-19.[10–12] Therefore, it is important to distinguish this 'pseudo-progression' in the setting of COVID-19 infection and vaccination as it impacts decisions around commencement of CLL therapy. Relapses were common, with the two latter cases requiring R-CVP and rituximab, respectively, to manage their re-presentation with AIHA, whilst Case 1's representation was managed with prednisolone and IVIg.

Given this is a rare complication in uncommon diseases, further assessment of registry/population-based datasets will be helpful to gain more insight into incidence of this complication.

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Systemic mastocytosis with B-acute lymphoblastic leukaemia: clonal or coincidental?

To the Editor,

Systemic mastocytosis (SM) comprises a clinically diverse set of haematological malignancies characterised by clonal proliferation of abnormal mast cells (MCs) and, in >90% of cases, a gain of function mutation in *C-KIT* (*C-KIT* D816V).[1] An associated haematological neoplasm (SM-AHN) co-occurs in 20–40% of cases and is overwhelmingly of myeloid origin.[2] Herein, we report a case of SM-AHN with B-acute lymphoblastic leukaemia (B-ALL).

A 67-year-old male was referred for evaluation of fatigue, cytopenias and progressive spinal issues with pain, kyphosis and loss of height. There were no B symptoms, cutaneous symptoms, anaphylaxis or angioedema. Past medical history was significant for hypertension, diverticulosis, gastro-oesophageal reflux disease and a resected adrenal adenoma. Full blood count showed: Hb 102 g/L, MCV 103, platelets 110×10^9/L, neutrophils 0.7×10^9/L. There was no eosinophilia or circulating blasts. Computed tomography (CT) of neck/chest/abdomen/pelvis showed multiple vertebral crush fractures and diffuse osteopenia without lymphadenopathy or hepatosplenomegaly.

Bone marrow aspirate and flow cytometry showed 88% B-lymphoblasts with the following immunophenotype: CD19+/CD20−/CD10v/SMIG−/cCD79aw/cCD22−/cIgM−/CD13+/CD33w/CD15v/MPO−/CD34+/HLADR+/TDT+. Although there were aberrant myeloid markers, the criteria for mixed phenotype acute leukaemia were not met. There were occasional hypogranular mast cells and no marrow eosinophilia. Bone marrow trephine was markedly hypercellular (~95%) with a heavy blastoid infiltrate. There were multi-focal clusters of spindle shaped MCs, each containing >15 cells and accounting for 5–10% of total cellularity (Fig. 1). Immunohistochemistry confirmed the flow cytometric immunophenotype of blast population with the addition of CD20+. The MCs were CD117+/tryptase+/CD2+/CD25+ (Fig. 1).

Fluorescent *in situ* hybridisation (FISH) was negative for BCR-ABL1 [t (9; 22)], KMT2A (11q23), FIP1L1-PDGFRA (4q12), PDGFRB (5q32), and FGFR1 (8p11) rearrangements. There were insufficient dividing cells for conventional cytogenetics. *C-KIT* D816V mutation was detected by allele-specific-polymerase chain reaction in unselected cells. Serum tryptase was modestly elevated at 17.1 µg/L (normal <13.5 µg/L), but less than the World Health Organization (WHO) specified diagnostic threshold (20 µg/L). Thus, the major and minor (3/4) WHO criteria for SM were met. The integrative diagnosis was SM-AHN with B-ALL.

Although the progressive vertebral crush fractures were suspected to be related to MC infiltrate, B-ALL was felt to be the dominant of the two pathologies and induction chemotherapy was commenced with cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD, A cycle). The disease was refractory to this treatment and alternative treatment options are now being considered.

To the authors' knowledge, this is the third reported case of adult SM-AHN with B-ALL and is unique in several ways.[3,4]

Firstly, AM-AHN typically involves myeloid malignancies (~90%): especially chronic myelomonocytic leukaemia; myeloproliferative neoplasms (MPN); myelodysplastic syndromes (MDS) and MDS/MPN overlap syndromes.[1,2] In these cases, SM and AHN are usually clonally related with *C-KIT* mutation demonstrated in both MC and AHN compartments. The developmental stage at which *C-KIT* mutation arises likely determines the phenotype and prognosis of SM, with indolent cases having *C-KIT* mutation only in MC and aggressive cases harbouring *C-KIT* mutation in stem cells and other lineages.[2,5] Lymphoid malignancies have rarely been reported with SM-AHN including chronic lymphocytic leukemia (CLL), atypical CLL, T-cell lymphoblastic lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma and splenic marginal zone lymphoma.[3,6–8]

Secondly, this case raises questions about the biological relationship between MC and lymphoid malignancies. In