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References

1. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;**18**:844–7.
2. Al-Samkari H, Karp Leaf R, Dzik W, Carlson J, Fogerty A, Waheed A, et al. COVID and coagulation: bleeding and thrombotic manifestations of SARS-CoV2 infection. *Blood*. 2020 [Online ahead of print]. https://doi.org/10.1182/blood.2020006520.
3. Zhang T, Sun LX, Feng RE. [Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019] [Article in Chinese]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;**43**:496–502.
4. Songping C, Shuo C, Xiunan L, Shi L, Feng W. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;**18**(6):1421–1424.
5. Klok F, Kruip M, van der Meer N, Arbous M, Gommers D, Kant K, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res*. 2020;**19**:148–50.
6. Stoneham SM, Milne KM, Nuttall E, Frew GH, Sturrock BR, Sivalo-ganathan H, et al. Thrombotic Risk in COVID-19: a case series and case-control study. *Clin Med*. 2020; [Online ahead of print]. https://doi.org/10.7861/clinmed.2020-0228.
7. McGonagle D, O'Donnell J, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatology*. 2020 [Online ahead of print]. https://doi.org/10.1016/S2665-9913(20)30121-1.
8. Middeldorp S, Coppens M, van Haaps TF, Foppen, M., Vlaar, A.P. & Müller, M.C. et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020 [Online ahead of print]. https://doi.org/10.1111/jth.14888.
9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;**395**:1054–62.
10. Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg B, Levin M, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol*. 2020;**76**:122–4. https://doi.org/10.1016/j.jacc.2020.05.001.
11. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The randomized embedded multifactorial adaptive platform for community-acquired pneumonia (REMAP-CAP) study: rationale and design. *Ann Am Thorac Soc*. 2020 [Online ahead of print]. https://doi.org/10.1513/AnnalsATS.202003-192SD.
12. Matsushita K, Ding N, Kou M, Hu X, Chen M, Gao Y, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. *medRxiv*. 2020 [Online ahead of print]. https://doi.org/10.1101/2020.04.05.20054155.

Successful treatment of chronic myelomonocytic leukaemia with hydroxycarbamide in a patient presenting with acute hypoxic respiratory failure due to COVID-19 pneumonia

On 30 March 2020, a 57-year-old male presented to our Emergency Department with a 6-day history of cough, persistent fever and worsening dyspnoea. His only known comorbidity was hypertension, managed with amlodipine and an angiotensin converting enzyme inhibitor. On admission, he was tachypnoeic and in severe hypoxic respiratory failure with dangerously low peripheral oxygen saturations (SpO_2) 83% on 15 l oxygen. Chest radiographic changes were consistent with COVID-19 infection and demonstrated bilateral changes with diffuse airspace shadowing with more confluence in the lower zones (Fig. 1A). Other relevant investigations included haemoglobin 127 g/l, white blood cell count (WBC) $117{\cdot}4 \times 10^9$/l, neutrophil count $32{\cdot}8 \times 10^9$/l, basophils $0{\cdot}4 \times 10^9$/l, lymphocytes $2{\cdot}7 \times 10^9$/l, monocytes $56{\cdot}1 \times 10^9$/l, platelet count 116×10^9/l, C-reactive protein 54 mg/l, lactic acid dehydrogenase 1732 U/l and D-Dimer 664 ng/ml.

COVID-19 was confirmed on SARS-CoV-2 real time reverse transcriptase polymerase chain reaction (RT-PCR) from a throat swab. The patient was immediately transferred to intensive care where he was intubated and ventilated and remained for 49 days. Ventilation proved difficult with rising oxygen requirements and decreased lung compliance. During the first week, his fraction of inspired oxygen (FiO_2) was consistently 0·6–0·75 and intermittently as high as 0·95 (i.e. 95% oxygen) with low and deteriorating PaO_2/FiO_2 ratios (Fig 2). This was consistent with severe acute respiratory distress syndrome (ARDS). He underwent multiple cycles of prone positioning and treatment with nitric oxide (a pulmonary vasodilator) in attempts to improve his oxygenation, and empirical treatment with antimicrobial agents, despite no definite evidence of bacterial co-infection. After a repeat chest X-ray demonstrated bilateral early fibrotic changes (Fig 1B), and with no improvement in gas exchange, methylprednisolone was commenced at 1 mg/kg twice a day for 10 days.

Profound leucocytosis was noted on admission, prompting investigation for an underlying haematological malignancy. Blood film showed increased monocytes, accounting for >40% of leukocytes with no excess blasts and promonocytes. Flow cytometry demonstrated a CD14- and CD64-positive monocytic population compromising 41% of total nucleated

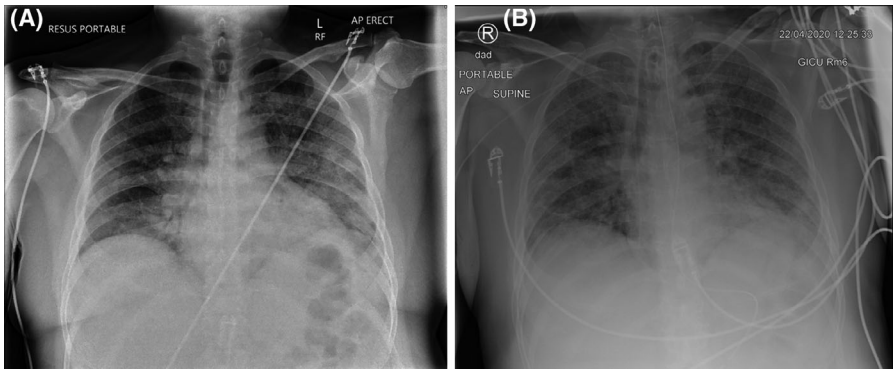

Fig 1. Chest X-Rays (A) on admission showing diffuse airspace shadowing throughout both lung fields more marked on the left with confluent shadowing in the lower zones bilaterally and (B) radiological deterioration on day 23 with more confluent airspace shadowing peripherally in the left lower zone.

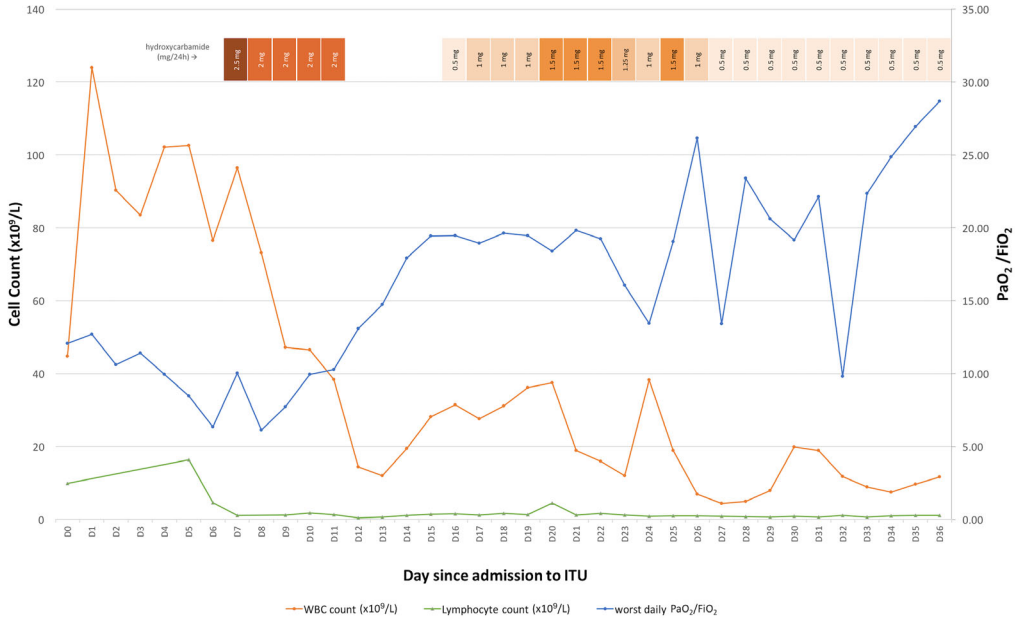

Fig 2. Trend in PaO_2/FiO_2, white blood cell and lymphocyte count with varying doses of hydroxycarbamide.

cells with no evidence of a CD34/117-positive myeloblast population. The patient was too unwell for an immediate bone marrow biopsy and had no historic full blood count. Fluorescent *in-situ* hybridisation (FISH) on peripheral blood showed no evidence of the high-risk abnormalities del(5q), del(7q) or del(17p). Molecular analysis identified *TET2*, *SRSF2* and *ASXL1* mutations by next-generation sequencing with no evidence of myeloproliferative neoplasms associated mutations. These findings were highly suggestive of chronic myelomonocytic leukaemia (CMML). Cytoreductive therapy was initially avoided due to concerns over myelosuppression during his critical illness. However, with persistent leucocytosis potentially contributing to on-going respiratory compromise, hydroxycarbamide was started on day 8. There was a good response with an improvement of WBC to 47×10^9/l within 48 h and white count suppression to $<10 \times 10^9$/l within 5 days. Subsequently, treatment was titrated to the WBC with 24 h dosing ranging from 500– 1500 mg with a target WBC of $25–35 \times 10^9$/l. The dose was adjusted carefully to ensure he did not develop severe myelosuppression. Throughout treatment, his neutrophils count remained $>2{\cdot}0 \times 10^9$/l. On day 24, during treatment with hydroxycarbamide, he developed a new onset nosocomial respiratory tract infection (probably secondary to a candida albicans) that responded well to 14 days of Fluconazole 400 mg. He made steady progress and required a tracheostomy on day 23 to aid respiratory weaning from the ventilator. He was decannulated on day 45 and subsequently discharged to the

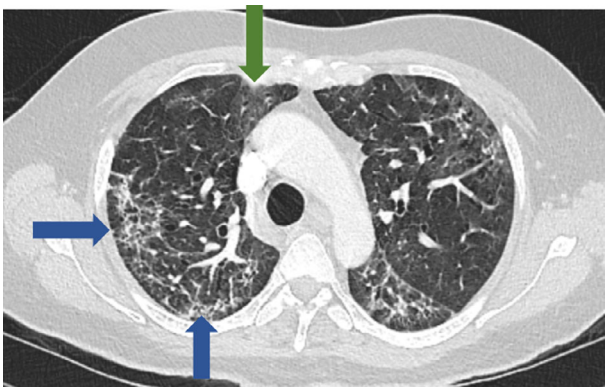

Fig 3. Computed tomography scan of the thorax on day 57 from admission, showing subpleural fibrotic appearance (blue arrows) and patchy ground glass changes (green arrow) without any focal consolidations.

ward on day 49. He had multiple SARS-CoV-2 RT-PCR assessments during his hospital admission and continued to be positive for SARS-CoV-2 viral ribonucleic acid (RNA) even until day 31. Subsequent multiple testing from day 36 onwards revealed no further detectable SARS-CoV-2 viral RNA from his respiratory samples. He also had a computed tomography scan of his thorax on day 57, which demonstrated bilateral peripheral or subpleural fibrotic changes with associated ground glass appearances without overt consolidations (Fig 3). These changes were thought to be consistent with a recent COVID-19 infection. When clinically well enough, he had a bone marrow biopsy which confirmed a diagnosis of CMML-1 with 3% blasts/promonocytes by morphology; karyotype was normal. After now successfully leaving hospital, he continues to make good progress in his physical recovery and will be reviewed in the haematology outpatient clinic for longer-term management of his CMML.

Discussion

Here we report the first case where COVID-19 unexpectedly presented concurrently with an underlying haematological malignancy, with profound hypoxaemia, leucocytosis and lymphopenia, resulting in a prolonged duration of mechanical ventilation in intensive care. To our knowledge, this is also the first report of successfully and safely using hydroxycarbamide during active COVID-19 infection.

Although the patient's acute severe hypoxaemic respiratory failure was initially thought to be secondary to COVID-19, the markedly elevated WBC of $>100 \times 10^9$/l on admission could have contributed significantly to his continued and marked hypoxaemia. Trends in WBC correlate well with levels of oxygenation; the most elevated WBC ($80–100 \times 10^9$/l) corresponded to the patient's most severe period of hypoxaemia. Within 48 h of initiating hydroxycarbamide, improvement was seen in his WBC, correlating with improving hypoxemia, as indicated by an increasing PaO_2/FiO_2 ratio. However, unlike the profound hypoxaemia usually seen with COVID-19 infection, extreme leucocytosis can be associated with 'spurious hypoxaemia' – a well-recognised phenomenon (particularly with a WBC $>100 \times 10^9$/l) where the SpO_2 is preserved despite an apparently low PaO_2 on blood gas analysis.[1,2]

The characteristic of CMML is a persistently raised peripheral blood monocyte count of $\geq 1{\cdot}0 \times 10^9$/l that accounts for ≥10% of leucocytes, according to World Health Organization diagnostic criteria.[3] The level of WBC is typically raised during intercurrent infections and in severe cases, hyperleucocytosis can occur causing end organ damage. The increase in WBC can accumulate in small vasculatures, particularly renal, cerebral, cardiac and pulmonary. If the COVID-19 pandemic had not occurred, pulmonary leucostasis would be one of the main differential diagnoses of the patient's presentation. The mainstay treatment of pulmonary leucocytosis is to reduce the WBC to improve oxygenation. There is currently limited published evidence on the safety of hydroxycarbamide use in patients with COVID-19 infections in view of its myelosuppressive effect. The other alternative considered was leukapheresis. However, there is a paucity of evidence on whether lowering the WBC in a short period of time improves overall survival, especially in the context of CMML.[4] On balance, it was felt that the mortality risk associated with pulmonary hyperleucostasis was high and cytoreduction therapy with hydroxycarbamide was started cautiously. More intensive chemotherapy was not an option as the patient was too unwell. As demonstrated, his lung perfusion improved with reduction of his WBC. He was concomitantly given antibiotics to cover for bacterial infections.

The longer-term prognosis in CMML is evaluated using a variety of risk scores that incorporate both presenting haematological findings and molecular genetics.[5] The finding of *ASXL1* mutations does place the patient at a higher risk, but the co-existent presentation of COVID-19 means that conventional scoring using blood counts and lactate dehydrogenase could not be utilised in this case and poses potential difficulties in determining the longer-term risk and treatment strategy. Overall, we presented a case of previously undiagnosed CMML in an otherwise fit and healthy patient presenting with severe COVID-19 complications, compounded by hyperleucostasis. Hydroxycarbamide was shown to be effective and safe to use in this case with no major sequelae.

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Conflicts of interest

The authors declare no conflict of interest.

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References

1. Chillar RK, Belman MJ, Farbstein M. Explanation for apparent hypoxemia associated with extreme leukocytosis: leukocytic oxygen consumption. *Blood*. 1980;**55**(6):922–4.
2. Jasahui MP, Chug L, Steven D. Spurious hypoxemia. *Chest*. 2013;**144** (4):333A.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. *WHO Classification of Tumours of Haematopoeitic and Lymphoid Tissues* (Revised, 4th IARC: Lyon; 2017.
4. Korkmaz S. The management of hyperleukocytosis in 2017: do we still need leukapheresis? *Transfus Apher Sci*. 2018;**57**(1):4–7.
5. Patnaik MM, Tefferi A. Chronic myelomonocytic leukemia: 2018 update on diagnosis, risk stratification and management. *Am J Hematol*. 2018;**93** (6):824–40.

Ruxolitinib for tocilizumab-refractory severe COVID-19 infection

Whilst the majority of patients with COVID-19 infection have mild self-limiting symptoms, for some the SARS-CoV2 virus can trigger a severe hyperinflammatory syndrome that is life-threatening. Anti-IL6 therapy has shown promise in restraining this hyperinflammatory syndrome and whilst IL-6 is a pleiotropic mediator of the inflammatory response, redundancy within inflammatory pathways means that the use of such targeted monoclonal therapy may have too restricted a repertoire in some patients. We present the case of a 53-year-old haematopoetic stem cell transplant recipient who developed severe COVID-19 that was refractory to anti-IL6 therapy, but responded to JAK/STAT inhibition with ruxolitinib, demonstrating its safety and efficacy in this setting.

For the majority of patients, the natural course of COVID-19 infection is mild and self-limiting, but for some, the disease is severe and can be catastrophic.[1] There is mounting evidence that a viral-induced cytokine storm can drive a hyperinflammatory syndrome, and raised serum ferritin and IL-6 levels are associated with a worse outcome.[2] Whilst this phenomenon is not unique to the SARS-CoV-2 virus, a striking feature in this setting is the hypoxia and lung injury associated with it. Patients who develop respiratory failure and require ventilatory support have higher plasma levels of an array of inflammatory cytokines including IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα, and their presence is associated with an inferior outcome.[3] The manifestation of the COVID-19 hyperinflammatory syndrome is reminiscent of the cytokine release syndrome seen with chimaeric antigen receptor (CAR) T-cell therapy, and this has provoked the use of anti-IL6 therapy with promising results.[4,5] However, this approach directs therapy again a single facet of the immune response, and whilst IL-6 is a pleiotropic mediator of inflammatory signalling, this strategy may be too targeted. There is considerable redundancy in cytokine and inflammatory pathways, so inhibiting a single molecule may permit collateral pathways to continue to drive the hyperinflammatory response.

Ruxolitinib is a JAK1/JAK2 inhibitor indicated for the treatment of disease-related splenomegaly or constitutional symptoms in patients with myelofibrosis or polycythaemia vera. Whilst ruxolitinib also significantly reduces serum IL-6 levels and C-reactive protein (CRP) in patients with myelofibrosis,[6] the central role of the JAK/STAT pathways as downstream effectors of the inflammatory response means the end-effector responses are more far-reaching. JAK1 and JAK2 are critical regulators of IL-2, IL-5, IL-10 as well as many other cytokines implicated in the inflammatory response seen in COVID-19.[3,7] This, coupled with evidence of a rapid mode of action, with reports of cytokine-induced STAT3 phosphorylation being inhibited within 2 hours of administration,[8] means ruxolitinib may offer therapeutic potential in COVID-19 hyperinflammation.

We report the case of 53-year-old man who had a haploidential stem cell transplant for chronic myeloid leukaemia in blast phase in 2017. His post-transplant course had been complicated by both acute and chronic graft-*versus*-host disease requiring multiple treatments including corticosteroids,