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

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Dear Editor,

On 30th March 2020, a 57-year-old male patient presented to the Emergency Department with a 6-day history of cough, persistent fevers 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 (SpO₂) 83% on 15L 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 (Figure 1A). Other relevant investigations included haemoglobin of 127 g/L, white blood cell count (WCC) of 117.4 x10⁹/L, neutrophil count 32.8 x10⁹/L, basophils 0.4 x10⁹/L, lymphocytes 2.7 x10⁹/L, monocytes 56.1 x10⁹/L, platelet count 116 x10⁹/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 the 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 (FiO₂) was consistently 0.6–0.75 and intermittently as high as 0.95 (i.e. 95% oxygen), with low and deteriorating PaO₂/FiO₂ ratios (Figure 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 (Figure 1B), and with no improvement in gas exchange, methylprednisolone was commenced at 1 mg/kg BD 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 cells with no evidence of CD34/117 positive myeloblast population.** He 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 MPN 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 WCC to 47 x10⁹/L within 48h and white count suppression to <10 x10⁹/L within 5 days. Subsequently, treatment was titrated to the WCC with 24h dosing ranging from 500 – 1500mg, with a target WCC of 25-35 x10⁹/L. **The dose was adjusted carefully to ensure he did not develop severe myelosuppression. Throughout treatment, his neutrophils count remained >2.0 x10⁹/L.** On day 24, during treatment with hydroxycarbamide, he developed a new onset

nosocomial respiratory tract infection (likely secondary to a candida albicans) that responded well to fourteen days of Fluconazole 400mg. 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 ward on day 49. **He had multiple SARS-CoV-2 RT-PCR assessments during his hospital admission and was continued to be positive for SARS-CoV-2 viral 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 CT scan of thorax on day 57, which demonstrated bilateral peripheral or subpleural fibrotic changes with associated ground glass appearances without overt consolidations (Figure 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 with 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 haematology outpatient clinic for the longer-term management of his CMML.

Discussion

Here we report a case where COVID-19 unexpectedly presented concurrently with an underlying haematological malignancy; with profound hypoxaemia, leucocytosis and lymphopenia and 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 hypoxemic respiratory failure was initially thought to be secondary to COVID-19, the markedly elevated WCC of $>100 \times 10^9/L$ on admission could have contributed significantly to his continued and marked hypoxaemia. Trends in WCC correlate well with levels of oxygenation; the most elevated WCC ($80-100 \times 10^9/L$) corresponded to the patients' most severe period of hypoxaemia. Within 48 hours of initiating hydroxycarbamide, improvement was seen in WCC, correlating with improving hypoxemia as indicated by 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 phenomenon well

recognised (particularly with WCC > 100 x10⁹/L) where the SpO₂ is preserved despite an apparently low PaO₂ on blood gas analysis [1,2].

The characteristic of CMML is persistently raised peripheral blood monocyte count of ≥1.0 x10⁹/L that accounts for ≥10% of leucocytes by WHO diagnostic criteria [3]. The level of WCC is typically raised during intercurrent infections and in severe cases, hyperleucocytosis can occur causing end organ damage. The increase in WCC 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 WCC 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 paucity of evidence on whether lowering the WCC in a short period of time improves the 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 patient was too unwell. As demonstrated, his lung perfusion improved with reduction of his WCC. He was concomitantly given antibiotic to cover for bacterial infections.

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 in a higher risk group but the co-existent presentation of COVID-19 means that conventional scoring using blood counts and LDH could not be utilised in this case and poses potential difficulties in determining longer term risk and treatment strategy. Overall, we presented a case of a previously undiagnosed CMML in an otherwise fit and healthy patient presenting with severe COVID-19 complications compounded by hyperleucostasis. Hydroxycarbamide showed to be effective and safe to use in this case with no major sequelae.

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Caption for figures:

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

Figure 2: Trend in PaO₂/FiO₂, white blood cell and lymphocyte count with varying dose of hydroxycarbamide.

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

Conflict of interest

Authors declare no conflict of interest.

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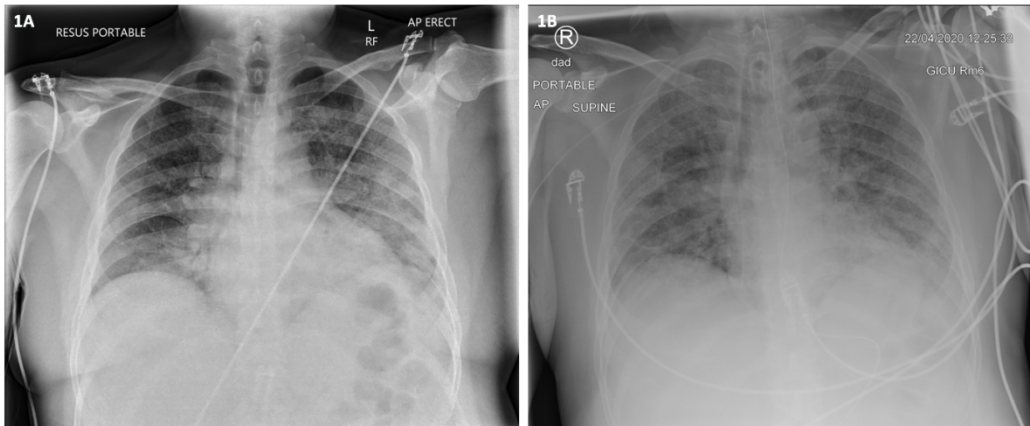


Figure 1. Chest X-Rays: (1A) on admission showing diffuse airspace shadowing throughout both lung fields more marked on the left with confluent shadowing in the lower zones bilaterally and (1B) radiological deterioration on D23 with more confluent airspace shadowing peripherally in the left lower zone

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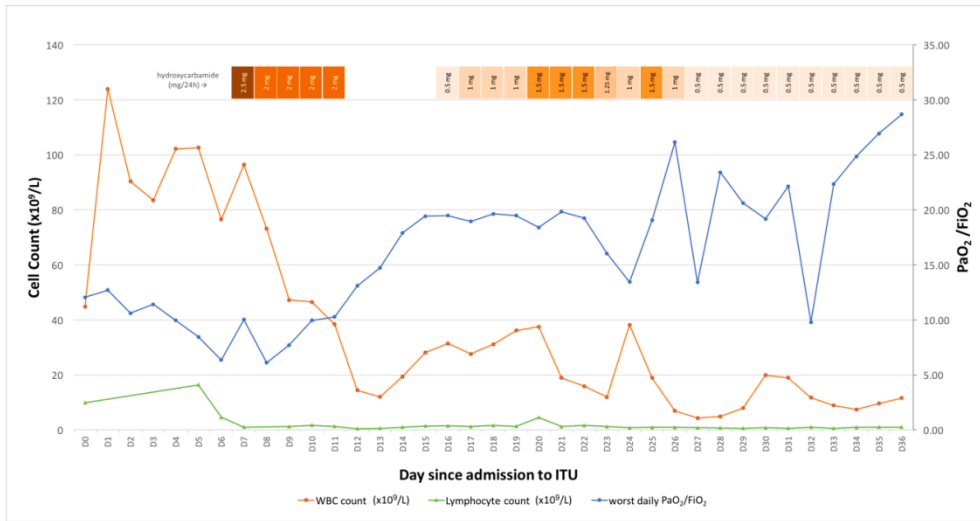


Figure 2. Trend in PaO₂/FIO₂, WCC and lymphocyte count with varying dose of Hydroxycarbamide

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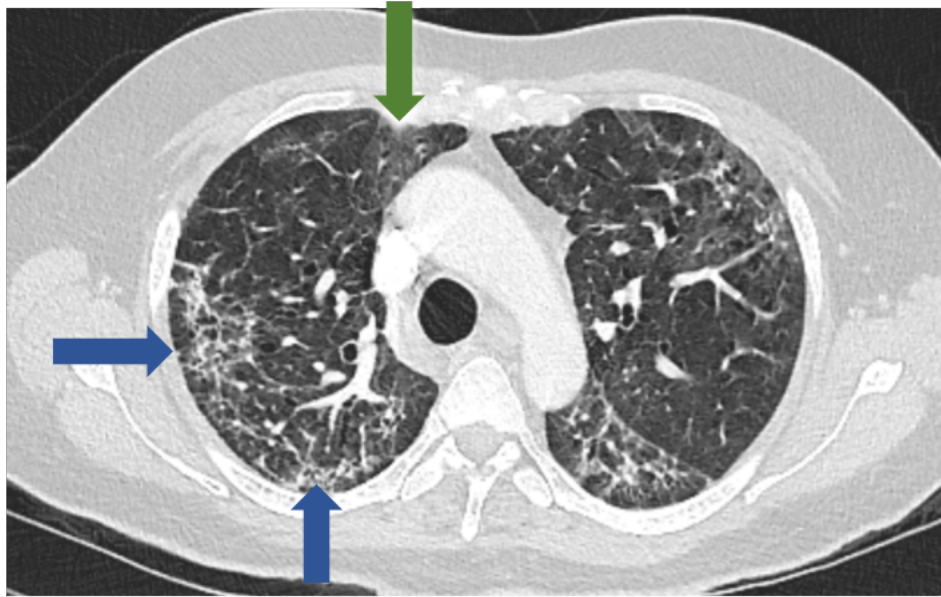


Figure 3: CT scan of thorax on day 57 from admission, showing subpleural fibrotic appearance (blue arrows) and patchy ground glass changes (green arrow) without any focal consolidations

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