

## Chronic lymphocytic leukaemia in COVID-19

Dear Editors,

COVID-19 has led to a global pandemic affecting the lives of millions of people around the world and causing hundreds of thousands of deaths. While leukaemia patients are regarded as an extremely vulnerable group, data on the impact of the current COVID-19 pandemic on them remain scarce. COVID-19 has been extensively reported to have a significant impact on the haematological and immune system. Lymphopenia has been one of the cardinal findings linked with the infection. However, the only patient profile presented with CLL and COVID-19 in literature has been the one of lymphocytosis.

We report the case of a 61-year-old patient with chronic lymphocytic leukaemia (CLL) who, with the diagnosis of COVID-19, experienced a spontaneous partial resolution of CLL lymphocytosis for a short period.

Maintaining a lymphocyte count above  $200 \times 10^9/L$  since 2017, the patient presented to the emergency unit on 13 April 2020 experiencing worsening type 1 respiratory failure and was determined to have a cytokine release syndrome grading of three. Her CLL was Binet stage A and was under surveillance, with progressive increase in white cell count (WCC) since July 2017, with a peak in January 2020 with WCC of  $213.8 \times 10^9/L$ .

She was admitted on the same day with a 7-day history of shortness of breath, cough and fatigue following a 2-week period of fever and productive cough. She tested positive for a COVID-19 swab, and a chest X-ray was performed (Figure 1). On 13 April 2020, her haemoglobin had reduced to 78 g/L, her white blood cell count reduced to  $84 \times 10^9/L$ , her d-dimer increased to 749 ng/mL, and her ferritin had increased to 809 ng/mL. The patient was transferred to the intensive care unit, given 1 unit of red blood cell transfusion and placed on 10 L/min of 60% oxygen. The patient was on amoxicillin-clavulanic acid started in community and was switched to piperacillin-tazobactam and clarithromycin on admission to intensive care where she was also given a tocilizumab infusion. Over the next few days, the patient's lymphocyte count fell to  $31.7 \times 10^9/L$ , which, albeit is still abnormally high, was low that the patient had not experienced since before her CLL diagnosis (Figure 2).

In fact, SARS-CoV-2 infection has been associated with lymphopenia amongst non-CLL patients, and it has been suggested to be a reliable predictor of COVID-19 severity.<sup>1,2,3</sup> In a meta-analysis including 12 case studies and 2282 patients, Zhao et al<sup>4</sup> found that lymphopenia constitutes a crucial element of COVID-19 severity, associating a decreased lymphocyte count to a threefold increase in severity. The following has been explained and reported by other studies in terms of exhaustion of antiviral lymphocytes upon viral infection.<sup>4</sup>

However, in the two case reports that exist surrounding COVID-19 in patients with CLL, the contrary is suggested. Paneesha et al<sup>5</sup> report an average threefold increase in lymphocytes in four cases; three of which died a few hours, 4 days and 6 days later after diagnosis. Jin et al<sup>6</sup> also report lymphocytosis in a case with a 25-day delay in diagnosis. Both reports describe cases with likely late diagnosis of COVID-19, which is indicated by both the studies themselves and the abrupt mortality of patients after diagnosis.

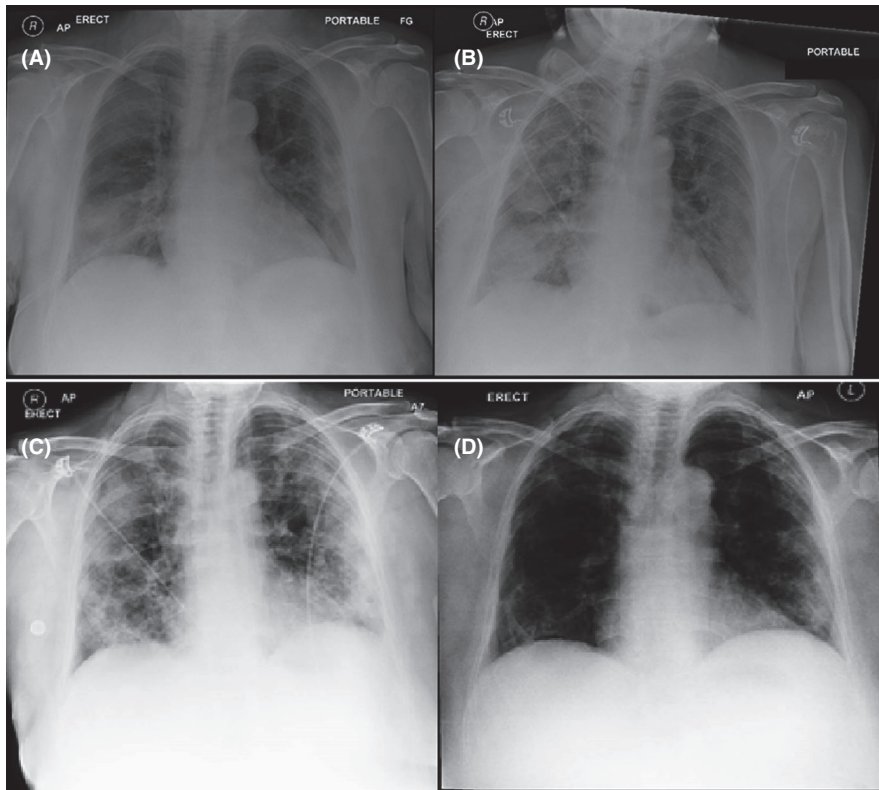
The clinical picture obtained from our patient indicates that upon earlier diagnosis, a significant resolution of lymphocytosis can be detected for a short period, but this may have been missed in current literature due to late diagnosis. Certainly, the lymphocytosis in this patient returned 6 days after admission, with lymphocytes increasing from  $31.7 \times 10^9/L$  to pre-COVID levels of  $>200 \times 10^9/L$  10 days later (Figure 2). However, a gradual and maintained decrease below  $200 \times 10^9/L$  was recorded shortly after, and this has continued until now, even with subsequent negative COVID-19 swabs.

However, the possible effects of the interleukin-6 (IL-6) inhibitor tocilizumab on CLL and the lymphopenia should not be ignored. IL-6 is generally considered as a B-cell growth factor, promoting tumour cell proliferation, survival, angiogenesis and immune suppression.<sup>7</sup> However, a vast plethora of recent studies suggest that IL-6 may have both pro- and antiproliferative properties on the tumour microenvironment.<sup>8</sup> Indeed, IL-6 was also found to be a key player in lymphocyte activation, proliferation and survival, thus potentially supporting protective antitumour immunity.<sup>8</sup> Nevertheless, the scale of the impact of tocilizumab on white blood cell count and in CLL patient has not been established yet with present contrasting evidence. While the use of Tocilizumab should be recognized as a confounding factor in our case, larger trials need to assess the interaction between COVID-19, interleukin-6 (IL-6) inhibition and CLL to provide optimal care for this vulnerable patient population.

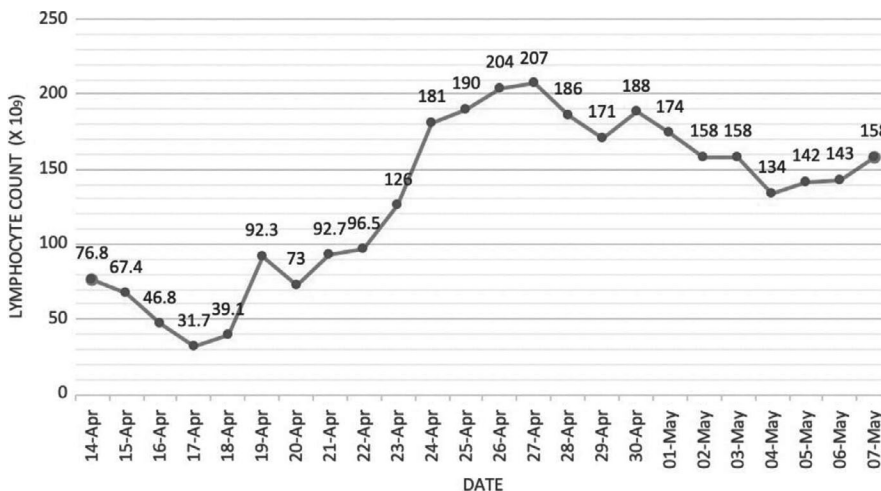
Overall, immediate increase in lymphocytosis must not be assumed in patients with CLL and COVID-19. Recommendations for early COVID-19 testing in CLL patients should be prioritized to ensure provision of optimal treatment and avoidance of late visualization of the infection peak. Furthermore, larger clinical trials are needed to assess the interaction between COVID-19, CLL and IL-6 inhibitors to ensure optimal provision of care in this vulnerable population.

### CONFLICT OF INTEREST

Mr Vardanyan, Mr Arjomandi Rad and Ms Wilson have nothing to disclose.



**FIGURE 1** A, Chest radiograph from 14 April 2020. There are lower lobe and peripheral predominant multiple opacities that are bilateral (>> unilateral) consistent with COVID-19. Disease extent: mild to moderate. B, Chest radiograph from 16 April 2020. There has been an increase in the bilateral airspace shadowing particularly on the right. Disease extent: severe. C, Chest radiograph from 27 April 2020. There is bilateral peripheral airspace opacification; some right-sided areas appear to have improved since 16 April 2020; however, some left-sided peripheral densities have progressed. D, Chest radiograph from 4 May 2020. There is patchy bilateral airspace consolidation, which has improved since the previous radiograph



**FIGURE 2** Lymphocyte count graph from ICU admission

## AUTHOR CONTRIBUTIONS

All authors contributed to the collection of data and manuscript development. Mr Vardanyan, Mr Arjomandi Rad and Ms Wilson designed the research study and analysed the data. Mr Vardanyan and Mr Arjomandi Rad wrote the paper.

## CONSENT

Written patient consent was obtained for the publication of clinical images and data.

## KEYWORDS

chronic lymphocytic leukaemia, COVID-19, lymphocytosis

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