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Covid-19 infection in therapy-naive patients with B-cell chronic lymphocytic leukemia

The global pandemic of the novel coronavirus SARS-CoV-2 represents one of the greatest infectious challenges to human health in recent history [1]. At the current time over 3.2 million people have been infected and this has proved fatal in over 230,000 cases. Patients who are immune suppressed, from underlying disease or iatrogenic intervention, are believed to be at increased risk of severe clinical outcome and this is undergoing careful monitoring [2]. B cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common lymphoid malignancy in many countries and is seen primarily in older people. CLL is associated with significant immune suppression and patients show impaired humoral and cellular immune responses to infectious challenge and vaccination [3]. The clinical complications of SARS-CoV-2 infection are complex and their pathophysiology is uncertain. It is currently unclear if patients with severe outcomes develop inadequate virus-specific immune responses or if immunopathology from exaggerated adaptive immunity may contribute to symptoms. As such, the clinical impact of infection in patients with CLL is uncertain and may relate to stage of disease management [4].

It is likely that patients who undergo immuno-chemotherapy as part of disease management will be at increased risk of clinical complications following SARS-CoV-2 infection. In contrast, Bruton tyrosine kinase inhibitors, such as ibrutinib and acalabrutinib, may actually have some protective effect and this is being explored in clinical studies [5]. However, most patients who receive a diagnosis of CLL do not receive treatment until disease progression. This “watch and wait” policy means that very large numbers of patients live with untreated CLL and generally it is regarded that their risk from infection is lower than those who have undergone therapeutic intervention, although still higher than age-matched controls. As such, the clinical outcome of SARS-CoV-2 infection in patients with therapy-naive CLL is an area of considerable importance. In this report we document four patients with untreated CLL who contracted SARS-CoV-2 infection confirmed by PCR on throat swab at admission. Their clinical course was severe with a high rate of mortality. In addition, an increase in the lymphocyte count, a phenomenon we term ‘Covid-Induced Lymphocytosis’, was observed in all cases with an average three-fold increase during Covid disease. These findings suggest that SARS-CoV-2 infection in patients with therapy-naive CLL may be associated with considerably greater clinical risk than seen in the general population and argue for strict enforcement of quarantine conditions.

1 A 49-year old man was diagnosed with CLL in 2000 but had never needed treatment. There was a history of CLL in a 1st degree relative. CT scan in 2019 showed enlarged lymph nodes in the neck, chest and abdomen and splenomegaly of 15.5 cm. There was no 17p or 11q abnormality on FISH. At outpatient clinic in March 2020 the patient was asymptomatic with Binet stage C disease. Full blood count (FBC) showed Hemoglobin (Hb) 137 g/l, White blood cell count (WBC) 32 $\times$ 10^9/l and platelets 96 $\times$ 10^9/l. Lymphocyte count was 30 $\times$ 10^9/l (Fig. 1A).

4 weeks later the patient was admitted with Covid-19 infection and respiratory failure. The C reactive protein (CRP) rose to a peak of 332 mg/L at 7 days after admission. The white cell count rose 6-fold to a peak of 202 $\times$ 10^9/l at day 3, of which 177 were lymphocytes. Flow cytometry analysis at that time revealed that 90% of lymphoid cells were CLL with a similar phenotype to that seen at diagnosis. The lymphocyte and white cell count then fell steadily down to baseline at day 10 as the patient continued supportive care and their condition improved.

2 An 81-year old man was diagnosed with CLL originally in June 2016. Flow cytometry revealed typical CLL phenotype of CD19 + CD5 + CD23 + . In February 2018 the patient developed auto-immune haemolytic anaemia with Hb 75 g/l and reticulocyte count of 342 $\times$ 10^9/l (Normal Range < 80) and positive Direct Coombs Test. This was treated with prednisolone for several months and then discontinued. At clinic visit 6 months prior to final admission the patient was asymptomatic with normal examination. The patient had mild congestive cardiac failure and took furosemide 40 mg/day. At that time Hb was 119 g/l, WBC 24 $\times$ 10^9/l and platelets 192 $\times$ 10^9/l. Lymphocyte count was 22 $\times$ 10^9/l (Fig. 1B).

The patient was admitted to hospital in March 2020 with a one-week history of cough, fever and coryzal symptoms. Examination revealed pyrexia and arterial oxygen saturation of 80-90% on high flow oxygen therapy. The CXR showed bilateral infiltrates and SARS-CoV-2 PCR was positive. Hb was 126 g/l, WBC 37.5 $\times$ 10^9/l (lymphocytes 32) and platelets 251 $\times$ 10^9/l. The lymphocyte count was markedly higher than it had been for 2 years when it had risen during steroid treatment. CRP was markedly elevated at 368 mg/l and liver function tests were deranged. The patient was treated with antibiotics and oxygen treatment but unfortunately did not respond to therapy and died after 4 days.

3 An 80-year old woman was originally diagnosed with CLL in March 2018. There was a history of hypertension and chronic infection that had required prolonged antibiotic treatment in 2019. At clinic one month prior to final admission the blood count showed Hb 85 g/l, WBC 274 $\times$ 10^9/l and platelets 127 $\times$ 10^9/l. The lymphocyte count was 235 $\times$ 10^9/l. Bulky lymphadenopathy on seen on CT. The CLL was considered to be progressive Binet stage C disease and the patient was being prepared for first line treatment (Fig. 1C).

Prior to this the patient was admitted with shortness of breath and fever due to Covid-19 disease. CRP on admission was markedly raised at 396 mg/l. At admission the Hb had fallen to 74 g/l with WBC 291 $\times$

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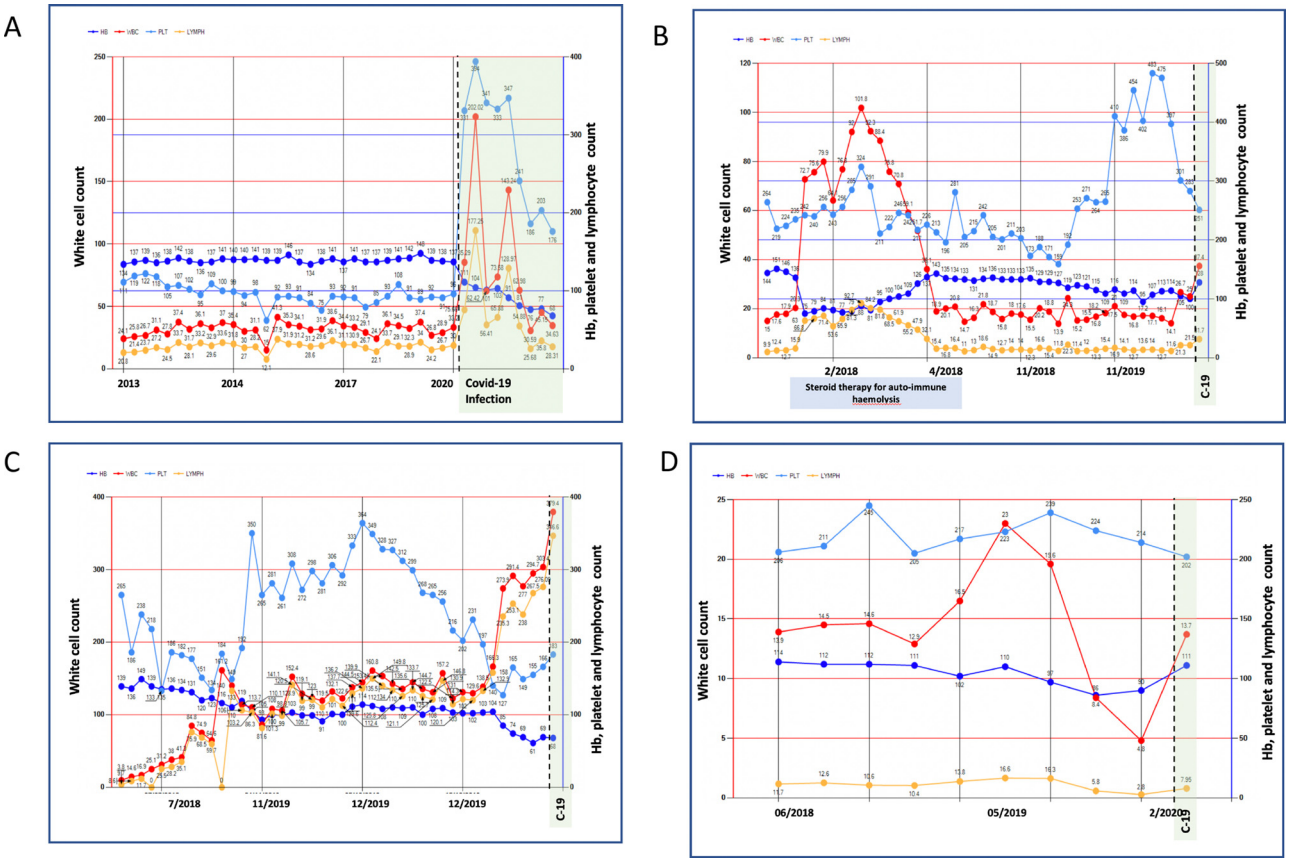

Fig. 1. Flow chart of blood count in each patient.
The x-axis shows the date (not to scale) and the period of Covid-19 infection is shown in green. The y-axis shows the total white cell count on the left-hand scale (WBC; x10^9/l) whilst the hemoglobin (HB; g/L), platelet count (PLT; x10^9/l) and lymphocyte count (LYMPH; x10^9/l) are shown on the right hand scale. HB is dark blue; WBC is red; Platelet count is light blue and Lymphocyte count is yellow. A, Case report 1; B, Case Report 2; C, Case Report 3 and D, Case Report 4.

10^9/l and platelets 165 × 10^9/l. The lymphocyte count was 253 × 10^9/l. Over the next 5 days the lymphocyte count rose to a peak of 346 × 10^9/l. Sadly, despite supportive treatment, the patient succumbed to infection after 6 days.

4 A 79-year old woman was diagnosed with CLL in June 2018. Flow cytometry revealed CLL with atypical immunophenotype (CD19 + CD5 + /-CD23 + /-CD79b-CD10-). Mantle cell lymphoma was excluded. The patient was otherwise well but had a 3-year history of diabetes mellitus and hypertension. Medication was gliclazide, metformin and losartan. The CT was normal. The patient developed iron deficiency anaemia in the 3 months prior to admission and was undergoing gastrointestinal investigation. The lymphocyte count had also fallen during this period and one month prior to final admission the blood count showed Hb 90 g/l, WBC 4.8 × 10^9/l and platelets 214 × 10^9/l. The lymphocyte count was 2.8 × 10^9/l (Fig. 1D).

The patient was admitted with acute respiratory symptoms 6 weeks later and was shown to be SARS-CoV-2 positive. At this time Hb was 111 g/l, WBC 13.7 × 10^9/l with lymphocyte count of 8 × 10^9/l. Biochemical profile was normal apart from albumin of 28 g/l. Sadly the patient died within a few hours of admission. As in all fatal cases in this series, autopsy was not performed.

There is currently considerable concern regarding the potential impact of SARS-CoV-2 infection in patients with malignant disease. In this report we discuss the clinical outcomes in four patients with untreated CLL following infection with the novel coronavirus. A striking feature was the clinical severity of infection with fatal outcome in three patients and severe disease in the fourth. At this time it is not possible to say that this definitively represents a more severe outcome than would be expected for patients within this age group. Three patients were aged over 75 years of age where the case fatality ratio from Covid-19 exceeds 8% [6]. In addition, these patients had some form of underlying health disorder including diabetes, hypertension or heart disease. Nevertheless, we were somewhat surprised to identify four patients with severe COVID-19 infection in this first wave of disease. Approximately 200 therapy-naïve CLL patients are seen locally and therefore this represents a case fatality of 1.5% . However, given that less than 5% of the UK population is believed to have become infected with the virus to date, these findings could represent a high degree of disease severity within CLL patients that do become infected. This will need to be examined in the large epidemiological studies which are now underway.

A second novel finding was the development of increased lymphocytosis in all patients at the time of acute SARS-CoV-2 infection. This is particularly surprising given that lymphopenia is an established correlate of severe and fatal Covid-19 disease in the general population [6–8]. Indeed, the average peak lymphocytosis in all 4 patients was 3-fold higher during SARS-CoV-2 compared to the most recent outpatient appointment (Fig. 2). This was particularly marked in patient 1 who displayed a 5-fold increase in the peripheral lymphocyte count and flow cytometry revealed that over 90% of these cells were from the original CLL tumour. This 'Covid-induced lymphocytosis (CIL)' is similar to that observed in patients who are treated with Prednisolone or inhibitors of Bruton tyrosine kinase although it was noteworthy that the CIL effect resolved within a few days. These drugs are believed to release CLL tumours cells from the bone marrow and secondary lymphoid tissue into the systemic circulation. At this stage the mechanism that underlies

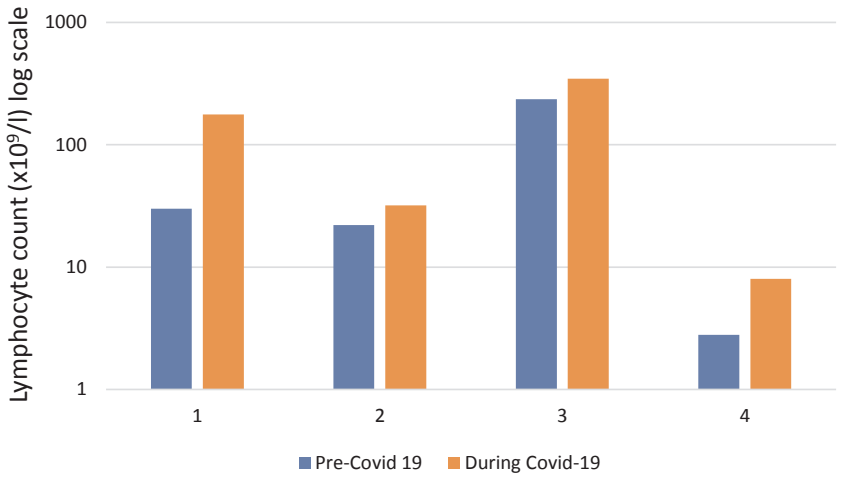

Fig. 2. Covid-induced lymphocytosis.
The peripheral lymphocyte count is shown for each patient at the most recent outpatient clinic prior to onset of SAR-CoV-2 infection and also the peak value during Covid-19 infection. The y-axis is a logarithmic scale.

Covid-induced lymphocytosis is unclear. It may result from very high levels of endogenous steroids during intense inflammation, but additional mechanisms may be in operation and deserve further investigation. Clinically, it is important to recognise that this is a feature of acute SARS-CoV-2 infection in patients with CLL and that the lymphocytosis can resolve quickly.

It is noteworthy that the severe outcomes observed were all in patients with untreated CLL, a group which typically is believed to be at somewhat lower risk of infectious complications compared to those with more advanced disease. However, it is well established that therapy-naïve patients do still have considerably increased infection risk compared to the general population [9]. Given the potential importance of immunopathological complications in severe COVID-19 disease it may be speculated that the relative residual immune-competence in untreated patients may place them at higher risk of severe disease, potentially even more so than those who are taking B cell receptor-targeting drugs. Patients on “watch and wait” management represent a large percentage of CLL patients and these observations suggest that these groups should be very carefully monitored during the ongoing SARS-CoV-2 pandemic and encouraged to continue self-isolating to limit exposure to viral infection.

Declaration of Competing Interest

The authors declare they have no competing interests.

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There are no acknowledgements.

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