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SARS-CoV-2 infection in aplastic anaemia

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The corona virus-induced disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by WHO in March 2020. Patients affected by hematological disorders have increased mortality and prolonged viral RNA persistence than patients with non-hematological cancers[1–3]. Since the early phase of the pandemic, several groups described thrombocytopenia or secondary hemophagocytic lymphohistiocytosis(sHLH) in patients affected by SARS-CoV-2 infection, and likely due to cytokine storm and the potential cytotoxicity of the virus[4,5].

Aplastic anemia(AA) a rare autoimmune disease, with incidence of 2/million, is characterized by cytopenia and bone marrow hypocellularity [6]. In acquired AA, it is proposed that an initiating event, provokes an aberrant immune response, triggering oligoclonal expansion of cytotoxic T cells that destroy haemopoietic stem cells.

The consequences of SARS-CoV-2 infection in known cases of AA are not clear[7]. Additionally, whether this viral trigger will induce an aberrant immune response leading to depletion of the stem cell compartment and inducing bone marrow failure (BMF) is unknown.

Herein we describe the features and clinical outcome of a group of patients affected with AA and SARS-CoV-2 infection between April 2020 and January 2021.

A national survey was launched between April 2020 to assess the clinical features and the outcome of patients with pre-existing AA and new onset AA after SARS-CoV-2 infection.

The diagnostic and severity criteria of AA were described previously by Camitta et al.[8]; the diagnosis of SARS-CoV-2 infection was confirmed on a nasopharyngeal swab[9] at the onset of symptoms or at access to the haematology department.

Twenty-three AA patients [30% very severe AA (VSAA), 26% severe AA (SAA) and 43% non-severe AA (NSAA)] with a median age of 49 (range 20 – 77), 7 females and 16 males was the study population. All cases were acquired, except one with Fanconi anaemia. Subclinical PNH clone were present in five cases.

At the onset of SARS-CoV-2 infection, 60% (14/23) of patients were on active immune suppressive therapy (IST): 6 on high dose ciclosporin (CSA) maintenance after ATGAM, one on eltrombopag and ciclosporin and 7 on a combination of ciclosporin and mycophenolate mofetil as part of GVHD prophylaxis after reduced-intensity allograft. Table 1 summarises the populations' demographic and allogeneic stem cell transplant details.

None of the patients were vaccinated against SARS-CoV-2.

The most common symptoms were fatigue, general malaise, fever, dry cough, shortness of breath, loss of smell, and diarrhoea; 29% (7/23) of patients who developed a COVID-19 defining event (6 pneumonia and one hepatitis) were hospitalized (median 5 days, range 3-12). Within this subgroup, 3 patients required oxygen supplementation, of which two needed escalation to the intensive care unit (ICU) for high flow oxygen and monitoring, but none required mechanical ventilation.

At diagnosis of the infection, median blood count parameters showed pancytopenia: white blood cells (WBC) 2,3 10^9/L (range 0,42 – 5,1, IQR 0,97), neutrophils 1,08 10^9/L (range 0,14 – 2,56, IQR

0,68) haemoglobin (Hb) 93,5 g/L (range 74 – 139, 25th centile 82, 75th centile 101) and platelets (Plt) 35 10^9/L (range 2-121, IQR 42). None developed evidence of sHLH.

Upon review of blood results pre-SARS-CoV-2 infection, it was possible to appreciate a progressive decline in all the haematological indices; consistent with overt relapse (confirmed by bone marrow hypocellularity meeting diagnostic criteria) in two patients and decline in blood parameters not meeting relapse criteria in 15 patients, but nevertheless requiring treatment, intense monitoring, and transfusion support.

Interestingly, 3 cases (12.5%) of idiopathic AA were diagnosed a few weeks after documented SARS-CoV-2 infection. The blood counts performed in the immediate past for other medical reasons showed normal parameters in all 3 SAA/VSAAA patients. They developed severe cytopenia with heavy transfusion dependency, and eventually required treatment with IST or HSCT(Table 1). At the time of reporting, all 3 patients are in remission with good haematological response.
Figure 1 shows the blood parameters and the median values of WBC, Hb, and Plt at three different time points (pre-infection, at infection, and post-infection) in the four groups of the study population: newly diagnosed, on active IST, off IST and post-HSCT.

For those patients affected by transfusion independent NSAA(10/23), there was a new requirement of transfusion support in 7 patients, but no case of transition to severe/very severe AA category was recorded.

Despite profound neutropenia and being on IST, COVID-19 developed only in 13% of patients(3/23). This may reflect some specific favourable host factors (such as young age) or might be secondary to protective immune dysregulation known to be present in AA[10]; indeed, hypotheses surrounding the role of hyperinflammation resulting in a more severe disease phenotype have resulted in trial proposals of agents blocking these pathways for treatment of severe SARS-CoV-2 infection in non-AA patients[11].

Here, despite the lack of cytokine studies or viral PCR on bone marrow aspirate, it is reasonable to speculate a potential myelosuppressive effect of SARS-CoV-2: as demonstrated in figure 1, there is a clear decline in haematopoiesis causing the worsening of the blood parameters and relapse of AA.

The nature of this study does not clarify if there is a direct cytotoxic effect on the haematopoietic stem cell from the virus or the cytokine storm or aberrant immune dysregulation following the viral infection and might have a bias due to non-reporting of milder cases.

We demonstrate that SARS-CoV-2 infection is another factor that can jeopardise the residual haematopoiesis during AA as previously described with other viral infections(i.e., hepatitis). The kinetics of FBC deterioration after SARS-CoV-2 infection mirrors the previous reports of AA diagnosis or relapse in pregnancy. Although a clear correlation between pregnancy and the onset or relapse of AA was never clearly demonstrated, several groups described worsening of hematological indices at the onset of pregnancy and its subsequent recovery in the post-partum period.[12,13].

This study does not allow to make a clear conclusion about the severity and long-term prognosis of SARS-CoV-2 infection in AA; despite the lack of COVID-19 deaths, the viral infection is either a risk factor for the onset of AA or for worsening of the blood parameters.

This is first report describing the outcome of AA following SARS-CoV-2 infection, and while encouraging to note that most patients(including those post-HSCT) made a full recovery without the development of significant symptoms, this population needs to be considered at risk of complications of worsening cytopenias following Covid-19 infection. Indeed, one patient died as consequence of infectious complications due to relapsed AA.

Also, a possible temporal relationship can be suggested in 3 cases between SARS-CoV2 infection and AA. Are these cases a casual association of SARS-CoV-2 infection and AA or secondary AA as a result of the viral insult? What is intriguing is the detection of 3 new AA within a total of 4.5 million cases of SARS-CoV-2 infection in the UK and if these new cases would happen regardless of the pandemic or are a direct consequence of the viral insult/trigger. Further studies that include measurement of cytokines and other factors such as regulatory T-cell subsets are needed to characterise the immune and inflammatory environment following SARS-CoV-2 infections in AA patients to help predict outcomes and prognosis. Also, considering the availability of vaccines to prevent SARS-CoV2 infection, it is important to prevent the cytopathic effect with a successful AA vaccination program, although close monitoring is required as vaccination induced AA has been reported in the literature.

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Table 1

AA disease characteristics at SARS-Cov-2 infection	N (%)
Number of patients (n, %)	23 (100)
Female	16 (70)
Male	7 (30)
Age, years (median, range)	49 (20-77)
Disease category	
VSAA	7 (30)
SAA	6 (26)
NSAA	10 (43)
Disease status (n, %)	
New onset/diagnosis	3 (13)
In remission	14 (60)
On treatment	7 (30)
On CSA post hATG	6 (26)
EPAG	1 (4)
Others*	6 (26)
Post-HSCT** on IST	7 (30)
SARS-CoV2 features (n, %)	
Mild	13 (57)
Moderate	7 (30)
Severe	3 (13)
Oxygen supplementation	3 (13)
Intensive care admission	2 (8)
AA status post SARS-CoV2	
New onset AA	3 (13)
Relapse of AA	1 (4)
Decline in hematological indices	15 (65)
Outcome of AA	
Death	1 (4)
New treatment	4 (17)
IST	3 (13)
HSCT	1 (4)

* Others- included patients who never required treatment for AA and also patients who had successful withdrawal of cyclosporine after achieving remission for their AA ** matched unrelated (n=3), matched sibling (n=2), mismatched unrelated (n=1), haploidentical (n=1); this group includes patient who had either upfront transplant or at failure of immune suppressive therapy

VSAA- very severe aplastic anemia, SAA- severe aplastic anemia, NSAA- non severe aplastic anemia
CSA- cyclosporin, EPAG- eltrombopag, ATG- anti-thymocyte globulin, HSCT- hematopoietic stem cell transplant, IST- immunosuppressive therapy

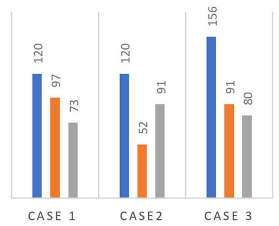
Legend

Figure 1: Haematological parameters in AA and SARS-CoV-2 infection

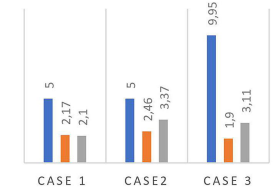
This shows the blood parameters and the median values of WBC (x 10^9/l), Hb (g/l), and Plt (x 10^9/l) at three different time points (pre-SARS-CoV2 infection, during the time of infection, and post-infection) in the four groups of the study population: newly diagnosed AA, AA on active IST, off IST and post-HSCT. Note complete data for some of the blood parameters was not available in 4 cases, and hence excluded from the graphical illustration

NEW DIAGNOSIS

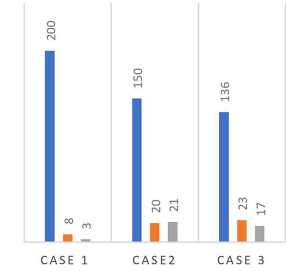
HAEMOGLOBIN



WHITE BLOOD CELL

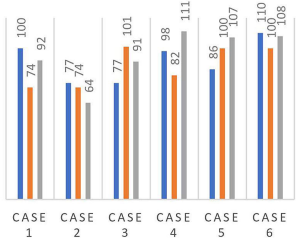


PLATELETS



AA IN TREATMENT

HAEMOGLOBIN



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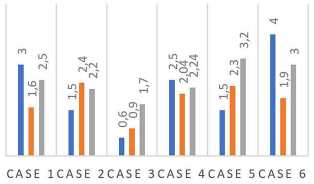

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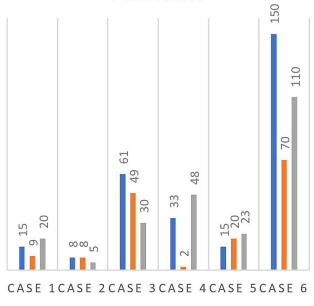
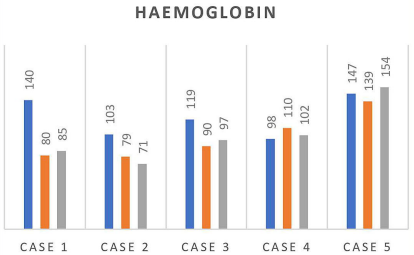


AA OFF TREATMENT

HAEMOGLOBIN



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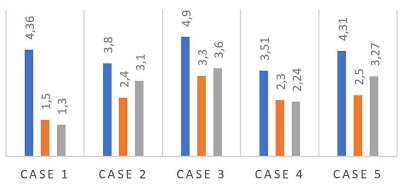

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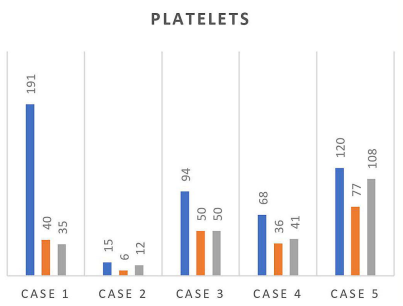

POST-HSCT

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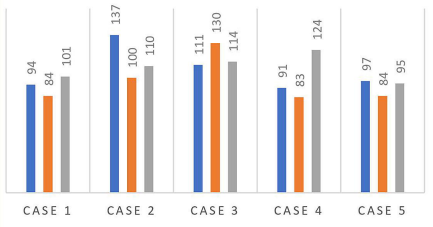

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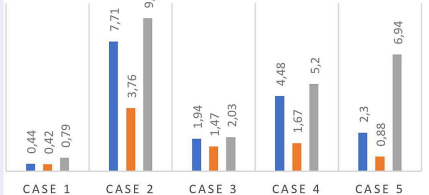

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