SARS-CoV-2 infection in aplastic anemia

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization in March 2020. Compared to patients with non-hematologic cancers, patients affected by hematologic disorders have increased mortality and more prolonged viral RNA persistence.[1-3] Since the early phase of the pandemic, several groups have described thrombocytopenia or secondary hemophagocytic lymphohistiocytosis in patients infected by SARS-CoV-2, problems likely due to a cytokine storm and the potential cytotoxicity of the virus.[4,5]

Aplastic anemia (AA), a rare autoimmune disease with an incidence of two cases per million population, is characterized by cytopenia and bone marrow hypocellularity.[6] It has been proposed that, in acquired AA, an initiating event provokes an aberrant immune response, triggering oligoclonal expansion of cytotoxic T cells that destroy hematopoietic stem cells.

The consequences of SARS-CoV-2 infection in known cases of AA are not clear.[7] Additionally, it is unknown whether this virus can trigger an aberrant immune response leading to depletion of the stem cell compartment and inducing bone marrow failure. Here 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 in April 2020 to assess the clinical features and outcome of patients with pre-existing AA and new onset AA after SARS-CoV-2 infection. The criteria for diagnosing AA and classifying its severity were described previously by Camitta *et al.*[8] The diagnosis of SARS-CoV-2 infection was confirmed by nasopharyngeal swab[9] at the onset of symptoms or at access to the hematology department.

The study population consisted of 23 patients with AA (30% with very severe AA, 26% with severe AA and 43% with non-severe AA) with a median age of 49 years (range, 20–77); there were seven females and 16 males. All cases were acquired, except one with Fanconi anemia. A subclinical paroxysmal nocturnal hemoglobinuria clone was present in five cases. None of the patients was vaccinated against SARS-CoV-2.

At the onset of SARS-CoV-2 infection, 60% (14/23) of the patients were on active immunosuppressive therapy – six on high-dose cyclosporine maintenance treatment after horse antithymocyte globulin, one on eltrombopag and cyclosporine and seven on a combination of cyclosporine and mycophenolate mofetil – as part of graft-*versus*-host disease prophylaxis after a reduced-intensity allograft. Table 1 summarizes the populations' demographic and allogeneic stem cell transplant details.

The most common symptoms were fatigue, general malaise, fever, dry cough, shortness of breath, loss of smell, and diarrhea; 29% (7/23) of patients who developed a COVID-19-defining event (6 pneumonia and 1 hepatitis) were hospitalized (median 5 days; range, 3-12). Within this subgroup, three patients required oxygen supplementation, of whom two needed escalation to intensive care unit admission 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 $2.3x10^9$/L (range, 0.42–5.1; interquartile range [IQR], 0.97), neutrophils $1.08x10^9$/L (range, 0.14–2.56; IQR, 0.68), hemoglobin 93.5 g/L (range, 74–139; 25th percentile 82, 75th percentile 101) and platelets) $35x10^9$/L (range, 2-121; IQR, 42). None developed evidence of secondary hemophagocytic lymphohistiocytosis.

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

Interestingly, three cases (12.5%) of idiopathic AA were diagnosed a few weeks after documented SARS-CoV-2 infection. Blood counts performed in the immediate past for other medical reasons showed normal para meters in all these three patients, who developed severe or very severe AA with heavy transfusion dependency, and eventually required treatment with immunosuppressive therapy or hematopoietic stem cell transplantation (Table 1). At the time of reporting, all three patients are in remission with good hematologic response.

Figure 1 shows the median values of white blood cell

Table 1. Characteristics of the patients with aplastic anemia at the time of infection with severe acute respiratory syndrome coronavirus-2.

AA disease characteristics at SARS-Cov-2 infection	N (%) or median [range]
Number of patients (n, %)	23 (100)
Female	16 (70)
Male	7 (30)
Age in years, median [range]	49 [20-77]
Disease category, n (%)	
Very severe AA	7 (30)
Severe AA	6 (26)
Non-severe AA	10 (43)
Disease status (n, %)	
New onset/diagnosis	3 (13)
In remission	14 (60)
On treatment	7 (30)
On CSA after hATG	6 (26)
Eltrompopag	1 (4)
Others*	6 (26)
Post-HSCT** on IST	7 (30)
SARS-CoV2 features	**N (%)**
Severity	
Mild	13 (57)
Moderate	7 (30)
Severe	3 (13)
Oxygen supplementation	3 (13)
Intensive care admission	2 (8)
AA status after SARS-CoV2	
New onset AA	3 (13)
Relapse of AA	1 (4)
Decline in hematologic 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 aplastic anemia (AA) and also patients whose cyclosporine was successfully withdrawn after they had achieved remission of their AA. **Matched unrelated (n=3), matched sibling (n=2), mismatched unrelated (n=1), and haploidentical (n=1); this group includes patients who underwent transplantation either upfront or at failure of immunosuppressive therapy. AA: aplastic anemia; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; CSA: cyclosporine A; hATG: horse antithymocyte globulin; HSCT: hematopoietic stem cell transplant, IST: immunosuppressive therapy.

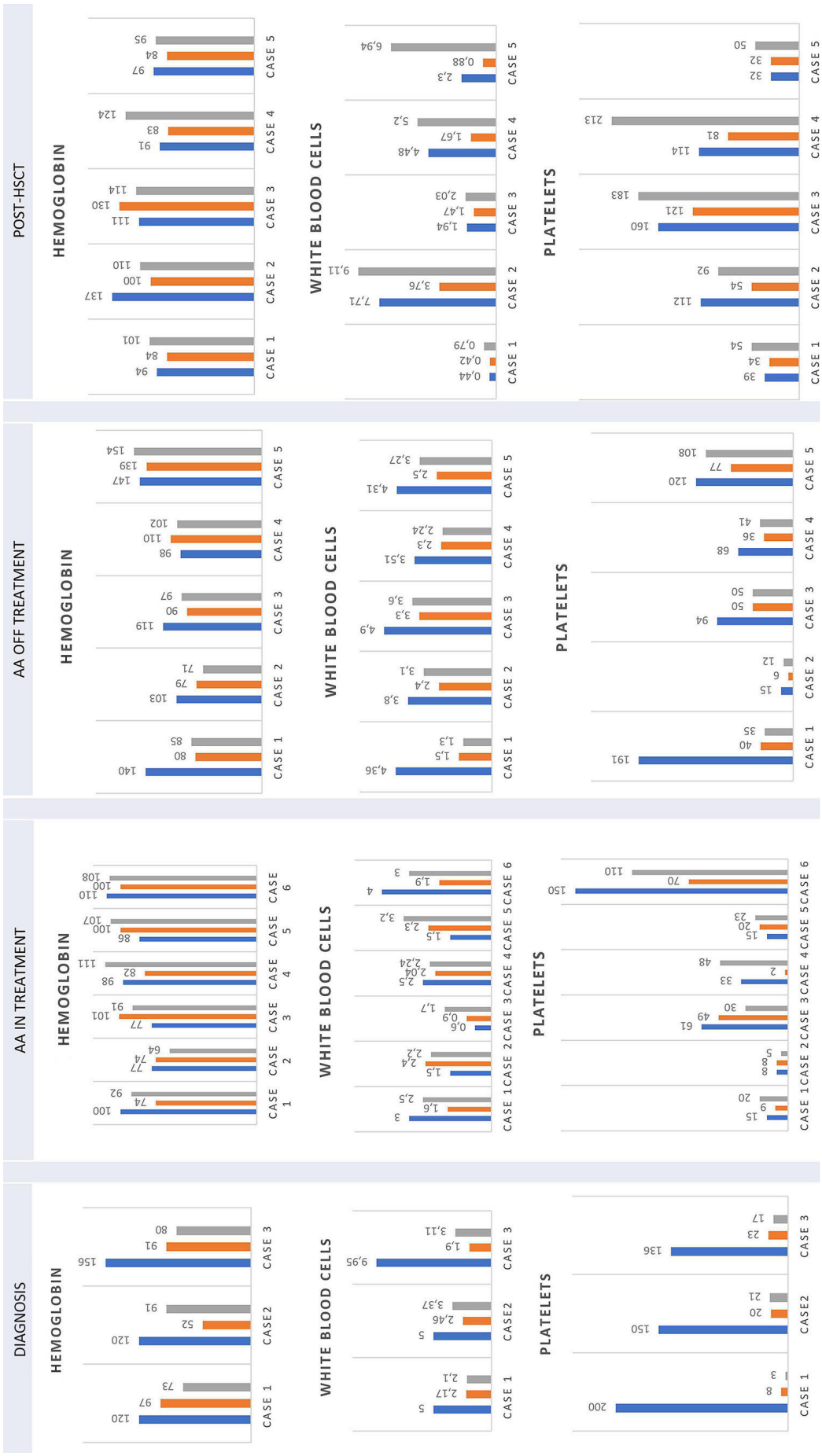

Figure 1. Hematologic parameters in patients with aplastic anemia and SARS-CoV-2 infection. Median values of white blood cell count (x10^9/L), hemoglobin (g/L), and platelet count (x10^9/L) at three different time-points (before, during and after SARS-CoV2 infection) in the four groups of the study population: (newly diagnosed aplastic anemia [AA], AA on active immunosuppressive therapy [IST], AA off IST and after hematopoietic stem cell transplantation [post-HSCT]). Note complete data for some of the blood parameters were not available in four cases, which were, therefore, excluded from the graphical illustration.

count, hemoglobin concentration and platelet count at three different time-points (pre-infection, at infection, and post-infection) in the four groups of the study population: newly diagnosed, on active immunosuppressive therapy, off immunosuppressive therapy and after hematopoietic stem cell transplantation.

For those patients affected by transfusion-independent non-severe AA (10/23), there was a new requirement of transfusion support in seven patients, but no cases of transition to severe/very severe AA were recorded.

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

Despite the lack of cytokine studies or viral polymerase chain reaction analysis of bone marrow aspirates in our study, it is reasonable to speculate a potential myelosuppressive effect of SARS-CoV-2: as demonstrated in Figure 1, patients had a clear decline in hematopoiesis, causing worsening of blood parameters and relapse of AA. However, the study does not clarify whether the virus has a direct cytotoxic effect on hematopoietic stem cells or acts through the cytokine storm or aberrant immune dysregulation following the 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 jeopardize residual hematopoiesis during AA, as previously described for other viral infections (e.g., hepatitis). The kinetics of the deterioration in blood counts after SARS-CoV-2 infection mirrors the previously reported kinetics of AA diagnosis or relapse in pregnancy. Although a clear correlation between pregnancy and the onset or relapse of AA has never been demonstrated, several groups have described worsening of hematologic indices at the onset of pregnancy and subsequent recovery in the post-partum period.[12,13]

Our study does not enable clear conclusions to be drawn about the severity and long-term prognosis of SARS-CoV-2 infection in AA; despite the lack of COVID-19 deaths, the viral infection was a risk factor for the onset of AA and for worsening of blood parameters in patients already with AA.

This is the first report describing the outcome of AA following SARS-CoV-2 infection, and while it is encouraging to note that most patients (including transplanted cases) 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. Indeed, one patient died as a consequence of infectious complications due to relapsed AA.

A possible temporal relationship between SARS-CoV2 infection and AA can be suggested in three cases in our series. Are these cases a casual association of SARS-CoV-2 infection and AA or are they cases of secondary AA as a result of the viral insult? The detection of three new cases of AA within a total of 4.5 million cases of SARS-CoV-2 infection in the UK is intriguing. Further studies that include measurement of cytokines and other factors such as regulatory T-cell subsets are needed to characterize the immune and inflammatory environment following SARS-CoV-2 infections in AA patients to help predict outcomes and prognosis. Furthermore, considering the availability of vaccines against SARS-CoV2 infection, it is important to prevent cytopathic effects of the virus 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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