

## TO THE EDITOR:

## SARS-CoV-2 infection associated with aplastic anemia and pure red cell aplasia

Nicholas C. J. Lee,<sup>1,2</sup> Bhavisha Patel,<sup>3</sup> Aaron Etra,<sup>4</sup> Taha Bat,<sup>5</sup> Ibrahim F. Ibrahim,<sup>5</sup> Madhuri Vusirikala,<sup>5</sup> Mingyi Chen,<sup>6</sup> Flavia Rosado,<sup>6</sup> Jesse Manuel Jaso,<sup>6</sup> Neal S. Young,<sup>3</sup> and Weina Chen<sup>6</sup>

<sup>1</sup>Department of Internal Medicine, and <sup>2</sup>Department of Pediatrics, UT Southwestern Medical Center, Dallas TX; <sup>3</sup>Hematology Branch, National Heart, Lung, and Blood Institute, Bethesda, MD; <sup>4</sup>Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; and <sup>5</sup>Division of Hematology-Oncology, and <sup>6</sup>Department of Pathology, UT Southwestern Medical Center, Dallas, TX

Aplastic anemia (AA) is a rare life-threatening disorder characterized by pancytopenia and a hypocellular bone marrow.<sup>1</sup> Pure red cell aplasia (PRCA) is a more limited marrow failure syndrome, with primary reduction in red blood cell production and virtual absence of marrow erythroid precursors. Although the etiology of immune-mediated marrow failure is complex, preceding viral infections have been associated with AA and PRCA, including parvovirus B19, cytomegalovirus, and Epstein-Barr virus. We present 6 cases of new-onset marrow failure (AA or PRCA) presumably associated with preceding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

The records of patients treated for AA or PRCA at the University of Texas Southwestern, Parkland Hospital, the National Institutes of Health, and Mount Sinai were reviewed for SARS-CoV-2 infection. Six patients without prior hematologic diseases or SARS-CoV-2 vaccination were identified who had SARS-CoV-2 infection presumably before the diagnosis of AA or PRCA. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board (STU-2020-0832) and was performed according to the Declaration of Helsinki.

Patient #1 is a 22-year-old White woman who presented with fatigue and ecchymoses. She was positive for SARS-CoV-2 per results of polymerase chain reaction (PCR) testing 10 days before identification of pancytopenia, and AA was confirmed by using bone marrow biopsy results (5% cellularity) (Table 1). Her extensive workup, including HIV, viral hepatitis panel, immunoglobulins, vitamin B<sub>12</sub>, and folate, was unremarkable, and she underwent HLA-matched family donor hematopoietic stem cell transplant. She has had a complete hematologic response (CR) at 8 months and remains well at last follow-up.

Patient #2 is a 69-year-old Asian woman who presented with symptoms of fatigue and was found to be pancytopenic. Complete blood count from a few months prior was normal. Further workup was positive for SARS-CoV-2 PCR and negative for other viral and nutritional deficiencies. Her SARS-CoV-2 PCR cycle threshold was 36, and immunoglobulin G was positive, suggesting persistent viral shedding and remote infection. She did not have respiratory symptoms and was diagnosed with severe AA based on a hypocellular marrow and pancytopenia. She underwent treatment with cyclosporine, equine antithymocyte globulin (h-ATG), and eltrombopag. She has had a partial response to therapy at her last follow-up of 10 months. Patients #1 and #2 had bone marrow specimens stained for SARS-CoV-2 by immunohistochemistry that were negative.

Patient #3 is a 76-year-old White man who was diagnosed with COVID-19 four months before presenting with a non-ST-segment myocardial infarction and was found to be profoundly anemic, requiring packed red blood cell transfusion. He re-presented with chest pain 1 week later and was found to have transfusion-dependent anemia. A brief trial with the erythropoietin-stimulating agent darbepoetin alfa was unsuccessful. Extensive workup for malignancy (including thoracic and abdominopelvic CT imaging),

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The data that support the findings of this study are available from the corresponding author upon reasonable request (weina.chen@utsouthwestern.edu).

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**Table 1. Clinical and pathologic information for patients with SARS-CoV-2-related AA and PRCA**

Variable	Patients						Summary*
	1	2	3	4	5	6	
Severity of aplasia	SAA	SAA	PRCA	SAA	SAA	SAA	5 SAA, 1 PRCA
Age at diagnosis, y	22	69	76	21	69	28	49
Sex	Female	Female	Male	Male	Female	Female	2 male subjects/4 female subjects
Interval between positive PCR and pancytopenia	10 d	2 d	4 mo	0 mo¶	5 mo	3 mo	7 wk
CBC, ×10 <sup>9</sup> /L WBC/ANC/ALC/PLT	3.0/0.71/2.88/41	2.2/0.52/1.1/10	10.3/6.5/2.0/298	1.6/0.5/1.0/4	3.0/1.2/1.5/10	2.8/0.83/1.72/2	3.0/0.77/1.8/10
Hgb/MCV, g/dL, fL	7.4/86.5	8.0/97	5.9/92.5	3.5/92.5	11.2/94.9	3.3/77	6.7/92.5
Absolute reticulocyte count, ×10 <sup>12</sup> /L	0.0107 (low)	0.019 (low)	0.008 (low)	0.172 (low)	0.0226 (low)	0.04 (low)	0.021
RBC transfusion	Yes	Yes	Yes	Yes	No	Yes	5 yes/1 no
Platelet transfusion	Yes	Yes	No	Yes	Yes	Yes	5 yes/1 no
BMBx cellularity	5%	5%-10%	20%-30%†	<5%	5%	20%-30%	
PNH clones	NA	–	–	5.2% (granulocytes), 32.7% (monocytes)	0.18% (granulocytes), 0.57% (monocytes), 0.02% (erythrocytes)	–	2/5: subclinical PNH clones
T-cell rearrangement	NA	NA	–	–	–	NA	3/3: –
NGS and CG	-(46,XX)	-(NA‡)	NA (46,XY)	NA (46,XY)	-(45,X-/46,XX)§	-(46,XX)	NGS 4/4: -CG 5/5: normal
Thrombotic events	–	–	–	–	–	–	6/6: –
History of autoimmune disease	–	–	–	–	–	–	6/6: –
Treatment	Sibling HSCT	CsA, h-ATG, EPAG	CsA—tacrolimus	CsA, h-ATG, EPAG	CsA, h-ATG, EPAG	CSA, h-ATG, EPAG	1/5: HSCT; 4/5: IST
Conditioning	Cy + h-ATG	NA	NA	NA	NA	NA	
GVHD PPX	FK/LD-MTX	NA	NA	NA	NA	NA	
Follow-up, mo	8	10	3	13	3	12	9
Ongoing treatment	Tacrolimus	CsA, EPAG	Tacrolimus	CsA	CsA, EPAG	CsA	6/6: Yes
Treatment response	CR	PR	CR	CR	NA	PR	3/5: CR
SARS-CoV-2 PCR (at diagnosis)	+	+	+	+	NA	NA	4/4: +
SARS-CoV-2 IgG	NA	+	NA	+	+	+	4/4: +
SARS-CoV-2 BMBx-IHC	–	–	NA	NA	NA	NA	2/2: –

VSAA was defined as an ANC < 200/μL. PR was defined as blood counts no longer meeting the standard Camitta criteria: ANC ≥ 500/μL, PLT ≥ 20 000/μL, and absolute reticulocyte count ≥ 60 000/μL. CR was defined as absolute ANC > 1000/μL, PLT ≥ 100 000/μL, and Hgb ≥ 10 g/L.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, peripheral blood cell count; CG, cytogenetics; CsA, cyclosporine; Cy, cyclophosphamide; EPAG, eltrombopag; FK, Tacrolimus; GVHD PPX, graft-versus-host disease prophylaxis; Hgb, hemoglobin; HSCT, hematopoietic stem cell transplant; IgG, immunoglobulin G; IST, immune suppressive therapy; LD-MTX, low-dose methotrexate; MCV, mean corpuscular volume; NA, not applicable; NGS, next-generation sequencing a large panel of genes in hematolymphoid neoplasms; PLT, platelet count; PR, partial response; SAA, severe AA; VSAA, very severe AA; WBC, white cell count.

\*Quantitative data presented as median.

†Marked erythroid hypoplasia.

‡No dividing cells found; could not evaluate karyotype.

§-X likely representing age-related changes.

||Bone marrow biopsy by immunohistochemistry (BMBx-IHC) used mouse monoclonal antibody against SARS-CoV/SARS-CoV-2 nucleocapsid protein (Sino Biological; 40143-MM05).

¶Although these patients had a short duration between positive PCR test results and observation of pancytopenia, their initial infections may be weeks to months before developing pancytopenia.

infection, and autoimmune etiologies was negative. The patient was diagnosed with acquired PRCA based on results of the bone marrow biopsy, and treatment was initiated with cyclosporine. He was transitioned to tacrolimus due to a medication interaction, and he has had a CR at 3 months and remains well at last follow-up.

Patient #4 was diagnosed with severe AA and pancytopenia with subclinical paroxysmal nocturnal hemoglobinuria (PNH) clones and COVID-19 infection; part of his clinical course was previously presented.<sup>2</sup> He had fatigue for 1 month and fever, chills, and sore throat 1 week before seeking medical care. Results of testing for

hepatitis, HIV, Epstein-Barr virus, and cytomegalovirus were negative. He was treated on a clinical trial (#NCT04304820) at the National Institutes of Health with cyclosporine and eltrombopag until SARS-CoV-2 PCR testing was negative, and then received h-ATG. He achieved a CR at 6 months and remains well at last follow-up. He showed expansion of his PNH clone requiring initiation of eculizumab, which adequately controlled intravascular hemolysis.

Patient #5 is a 69-year-old White woman who had mild COVID-19 infection managed at home 5 months before presenting with bruising and was found to have severe pancytopenia. Results of her

infectious, malignant, and autoimmune evaluations were negative, although she had minute PNH clones. The patient was diagnosed with platelet transfusion-dependent severe AA (5% cellularity on bone marrow); she initiated cyclosporine, h-ATG, and eltrombopag therapy <1 month ago, and it is too early to determine an immunosuppression therapy response.

Patient #6 is a 28-year-old woman who had COVID-19 and bruising 3 months before presenting with pancytopenia; part of her clinical course was previously reported.<sup>3</sup> Although her initial and repeat bone marrow biopsy specimens revealed 20% to 30% marrow cellularity, there was near absence of erythroid precursors and megakaryocytes, and the patient was dependent on packed red blood cell and platelet transfusion. There was no evidence of malignancy on cytogenetic array or next-generation sequencing assessment, and severe AA was suspected. No PNH clone was identified, and although telomere length was shorter than expected for age (less than the first percentile), there was no definitive evidence of inherited bone marrow failure syndrome on genetic sequencing assessment. She was treated with cyclosporine, h-ATG, and eltrombopag, and achieved transfusion independence.

All patients (2 male subjects/4 female subjects; median age, 49 years) described had pauci-symptomatic SARS-CoV-2 infections, but they presented with cytopenia and were eventually diagnosed with AA or PRCA. The major differential diagnosis includes acquired marrow failure and hypocellular myelodysplastic syndrome. In the absence of morphologic dysplasia or abnormal chromosomal and molecular results, hypoplastic myelodysplastic syndrome was less likely.

We report 6 cases of new onset of acquired marrow failure in patients with SARS-CoV-2 infection. A similar case series was reported recently, including 4 adult cases of AA diagnosed a few weeks after SARS-CoV-2 infection<sup>4,5</sup> and 2 pediatric AA cases with concomitant SARS-CoV-2 infection.<sup>6</sup> These are possibly coincidental due to the high prevalence of SARS-CoV-2. However, based on the number of positive SARS-CoV-2 test results in the 2021 Dallas–Fort Worth catchment area, we would tentatively expect a case rate of 9 per million per year, which is higher than the typical Western incidence of ~2 per million per year by several fold.<sup>7</sup>

For SARS-CoV-2 infection to initiate immune-mediated marrow failure, the infection would need to precede pancytopenia by weeks to months. Although one-half of our patients had a short duration between positive PCR test results and pancytopenia (patients #1, #2, and #4; range, 0-10 days), they oftentimes had no or minimal symptoms of respiratory COVID-19 infection; had positive test results by the elevated SARS-CoV-2 PCR cycle threshold and immunoglobulin antibodies, suggesting distant infection (patient #2); and/or presented with symptoms of pancytopenia such as fatigue and ecchymoses (patients #1, #2, and #4). Thus, in all 6 patients, we estimated that their initial SARS-CoV-2 infections were weeks to months before pancytopenia development, the symptoms of which often resulted in their presentation to care; they may remain persistently positive on PCR testing, as has been noted in patients with AA.<sup>2,5</sup>

Collectively, the epidemiologic data and preceding SARS-CoV-2 infection estimated to be weeks to months before developing

pancytopenia support the theory that SARS-CoV-2 may be causatively associated with AA. Moreover, there is evidence that COVID-19 pneumonia is a hyperinflammatory and immune dysregulated state, with improvement in survival with immunomodulatory treatments.<sup>8-11</sup> This case series does not provide a mechanistic link between SARS-CoV-2 infection and marrow failure, but it raises the possibility that SARS-CoV-2 may mediate an immunologic response or, less likely, a direct marrow toxicity that contributes to marrow failure. Patients appear to respond well to standard treatment (immunosuppression or marrow transplant) for AA.

In summary, we report the largest case series to date of new onset of AA and PRCA in adults, presumably associated with preceding SARS-CoV-2 infection, and their clinical outcomes. Further studies are needed to determine a definitive association and whether the natural history and response of marrow failure to standard therapy differ from those of idiopathic cases.

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**ORCID profiles:** N. C.J.L., 0000-0002-7478-8545; T.B., 0000-0002-8810-1038; M.C., 0000-0001-6754-0480; W.C., 0000-0001-5638-4371.

**Correspondence:** Weina Chen, Department of Pathology, University of Texas Southwestern Medical Center, BioCenter EB3.234, 2330 Inwood Rd, EB3.234, Dallas, TX 75390-9317; e-mail: weina.chen@utsouthwestern.edu.

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