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Acquired aplastic anemia following SARS-CoV-2 vaccination

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Abstract

COVID-19 is a potential life-threatening viral disease caused by SARS-CoV-2 and was declared a pandemic by the WHO in March 2020. mRNA-based SARS-CoV-2 vaccines are routinely recommended in immune-compromised patients, including patients with AA, as these patients are at increased risk of contracting COVID-19 and developing a more severe course of disease. Between March 2021 and November 2021 relapse of AA occurred in four (age [median]: 53 years, range 30–84 years) out of 135 patients currently registered at our department and two de novo cases of AA in temporal context to vaccination against SARS-CoV-2, were documented. Median time after first COVID-19 vaccination and relapse of AA was 77 days. All relapsed patients were vaccinated with the mRNA-based vaccine Comirnaty®. Relapse in two out of the four patients was refractory to CsA/eltrombopag, favoring IST with hATG/CsA or BMT, respectively. Our observations should prompt clinicians to take vaccine-induced relapse of AA or de novo AA after SARS-CoV-2 vaccination into account. Furthermore, careful clinical monitoring and vigilance for signs or symptoms that may indicate relapse of AA (e.g., bleeding complications) are indicated.

KEYWORDS
aplastic anemia (AA), relapse, SARS-CoV-2 vaccination

Novelty Statements

What is the new aspect of your work?

This is the first observational report in literature showing a possible association between relapse of aplastic anemia (AA) and coronavirus-induced disease 2019 (COVID-19) vaccination in a relevant number of patients. Furthermore, in two other patients, de novo diagnosis of AA was in timed context to COVID-19 vaccination. However, clinical interpretation of our data clearly requires caution as in none of the patients treated at our department, COVID-19 vaccine-independent relapse or de novo and/or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced AA can be excluded.
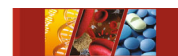
What is the central finding of your work?

Confirmed AA relapses were observed in four out of 135 patients with AA registered at our department. Median time after 1st COVID-19 vaccination and diagnosis of AA relapse was 77 days. All relapsed patients were vaccinated with an mRNA-based vaccine and in two out of these four patients, relapse was refractory to cyclosporine A (CsA)/eltrombopag, favoring immunosuppressive treatment (IST) with antithymocyte globulin (ATG)/CsA or bone marrow transplantation (BMT).

What is (or could be) the specific clinical relevance of your work?

Our observations should prompt clinicians to take vaccine-induced relapse of AA or de novo AA after COVID-19 vaccination as a possible vaccine-related adverse event into account and to inform patients about a potential risk for disease relapse following vaccinations.

1 | INTRODUCTION

Acquired aplastic anemia (AA) is a rare bone marrow failure (BMF) syndrome with an incidence of 2–3 cases/million inhabitants per year in Europe and the United States, but higher in East Asia.[1] The majority of cases are related to an autoimmune-mediated, T-cell-dependent destruction of early hematopoietic stem cells secondary to an initiating and in most of the cases (70%–80%) unknown event.[2,3] Disease severity and diagnosis is defined by the (modified) Camitta criteria, requiring at least two of the following criteria: 1. Neutrophils $<1.5 \times 10^9/l$ (non-severe AA (nSAA); severe AA (SAA) $<0.5 \times 10^9/l$; very severe AA (vSAA) $<0.2 \times 10^9/l$), 2. Platelets $<50 \times 10^9/l$ (nSAA; SAA and/or vSAA $<20 \times 10^9/l$) and/or 3. a reticulocyte count $<20 \times 10^9/l$). For SAA and vSAA, the criteria of a hypocellular bone marrow (histologically determined cellularity <25% or 25%–50% with a proportion of <30% hematopoietic cells in the bone marrow) must also be fulfilled; for nSAA, proof of a hypocellular bone marrow is sufficient.[3] This classification is of prognostic and therapeutic relevance. Depending on the affected hematopoietic lineages, disease-associated complications in patients with AA are iron overload secondary to red blood cell (RBC) comorbidity-adjusted transfusion-dependency and/or bleeding complications, due to thrombocytopenia, possible HLA (human leucocyte antigen) and non-HLA (minor histocompatibility) alloimmunization. Prolonged and/or severe neutropenia or immunosuppressive treatment (IST), even though antithymocyte globulin (ATG) and cyclosporine A (CsA) are not considered profoundly immunosuppressive, opposes patients at a greater risk for both, life-threatening infections in addition to reactivation of viral infections, especially following ATG therapy. Infection-related complications still remain one of the major causes of death in AA.[3]

On March 11, 2020, the World Health Organization (WHO) declared the coronavirus-induced disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic with first reports observed in Wuhan, Hubei province, China.[4] Since then, tremendous efforts have been made, which finally led to the development and authorized (emergency) use and/or approval of several SARS-CoV-2 vaccines by the European Medicines Agency (EMA) (mRNA-based: Comirnaty®, Spikevax®; viral vector-based: Vaxzevria®, Janssen) and the U.S. Food and Drug Administration (FDA) (Comirnaty®, Spikevax®, Janssen).[5,6]

Since the beginning of the SARS-CoV-2 pandemic, an increased risk in patients with AA of contracting a severe disease course in the event of COVID-19 has repeatedly been pointed out and led to the recommendation to favor vaccine administration in patients with AA.[7–9] However, appropriate timing of vaccination remains an important question, especially in patients on IST or post allogeneic stem cell transplantation, as efficacy data in these patients are limited. Moreover, whether these patients are even likely to mount an immune response to a vaccine is unclear.[8] If SARS-CoV-2 infection, even though not observed by Paton et al.,[10] might even be associated with a risk for overt relapse or could possibly serve as an initiating (post-infectious) event[11] for AA remains of further debate, despite rising evidence allowing to conclude a potential causative relationship.[12]

Of note, AA relapse or de novo AA can further be observed in a minority of patients postvaccination, especially following hepatitis B, influenza and varicella vaccination.[13–20] To the best of our knowledge, this is the first comprehensive report of possible COVID-19 vaccine-related AA relapse reported to date. Our data therefore highlight in conjunction with the observations made by Cecchi et al.,[21] Sridhara et al.,[22] and Tabata et al.[23] (all de novo cases of AA) the potential risk for contracting AA as a potential complication following vaccination against SARS-CoV-2 (vaccine-related adverse event).

2 | MATERIAL AND METHODS

2.1 | Study design

This is a single center, retro- and in part prospective, observational analysis in patients with confirmed AA relapse and de novo AA in timed context to SARS-CoV-2 vaccination conducted at the Department of Hematology and Stem Cell Transplantation at the University Hospital Essen, Germany. All suspected cases were previously reported to the Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut, PEI). The study was approved by the Ethics Committee of the University of Duisburg-Essen and conducted in accordance with the Declaration of Helsinki (21-10 318-BO). Written informed consent was obtained from the patients.

TABLE 1 Characteristics of patients with relapse of AA following COVID-19 vaccination (N = 4)

Patient	1	2	3	4
Gender	Male	Male	Male	Male
AA grade (age at diagnosis, yrs.)	nSAA (transfusion requirement for platelets and 2 pRBCs) (19)	nSAA with transition to SAA (82)	vSAA (47)	SAA (52)
PNH clone size at diagnosis (Gran., %, FLAER)	6.4	0.9	–	NV
Prior treatment for AA	• rATG (02/2011)/CsA (until 03/2015), re-initiation of CsA 10/2015 due to progressive, non-transfusion dependent thrombocytopenia	• hATG/CsA (04/2019)	• EPAG (due to severe atypical pneumonia at diagnosis (12/2017) • hATG/CsA/EPAG (01/2018) • Stem cell boost due to severe atypical pneumonia (02/18) • Switch to TAC/EPAG due to CsA-induced ARF (04/2018) (EPAG until 01/2019)	• hATG/CsA (02/2017) • EPAG (07/2017–09/2017)/CsA (until 10/2017) • EPAG/CsA due to AA relapse (05/2019) (EPAG until 01/2020)
AA-related therapy prior to vaccination	CsA	CsA	TAC	CsA
Relevant past medical history	–	–	FL (05/2004) Grade 1, III-SB (Ann Arbor staging classification) • 6 x CHOP-21 Relapse (06/2006) • 3 x R-ICE followed by autologous stem cell transplantation (CR)	–
Laboratory parameters 6 months before COVID-19 vaccination (mean)				
Hb (g/dl)	13.4	11.5	11.4	15.1
ANC (nl)	1.2	4.3	2.5	1.82
Platelets (nl)	84	135	151	89
ARC (nl)	69.8	52.8	69.3	73.5
Most recent laboratory parameters before COVID-19 vaccination				
Days	6	1	86	43
Hb (g/dl)	13.5	11.8	11	15
ANC (nl)	1.2	4.2	2.5	2.1
Platelets (nl)	88	145	156	81
ARC (nl)	79.7	54.6	64	69
COVID-19 vaccine	Comirnaty®	Comirnaty®	Comirnaty®	Comirnaty®
Most recent laboratory parameters post first COVID-19 vaccination				
Days	29	–	13	6
Hb (g/dl)	13.1	–	10.5	14.9
ANC (nl)	1.2	–	2.8	2.9
Platelets (nl)	76	–	143	81

2.2 | Disease-related definitions, methods, treatments

Relapse of AA or de novo AA was diagnosed, graded, and treated according to established guidelines.[3,24,25] PNH clone size was determined by flow cytometry and expressed as the percentage of fluorescein-labeled proaerolysin (FLAER)-negative granulocytes.[26] Clonal hematopoiesis (cytogenetic abnormalities and acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS)-associated somatic mutations; Medical Care Center Dr Eberhard and Partner Dortmund) suggestive of late clonal diseases in addition to histological examination of bone marrow, despite persistence of a hypocellular bone marrow in patients with stable remission of AA might even be observed, were excluded in all patients.

Quantitative determination of immunoglobulin G (IgG) antibodies against the SARS-CoV-2 spike protein (anti-SARS-CoV-2 S antibody levels) were determined in-house at the Institute of Virology of the University Hospital Essen from serum of our patients using the LIAISON SARS-CoV-2 TrimericS IgG kit (DiaSorin, Saluggia, Italy) according to the manufacturer's instructions. Measurement range of this chemiluminescence immunoassay (CLIA) is from 4,81 to 2080 binding antibody units (BAU/ml). Values ≥33,8 BAU/ml were considered positive.

2.3 | Statistical analysis

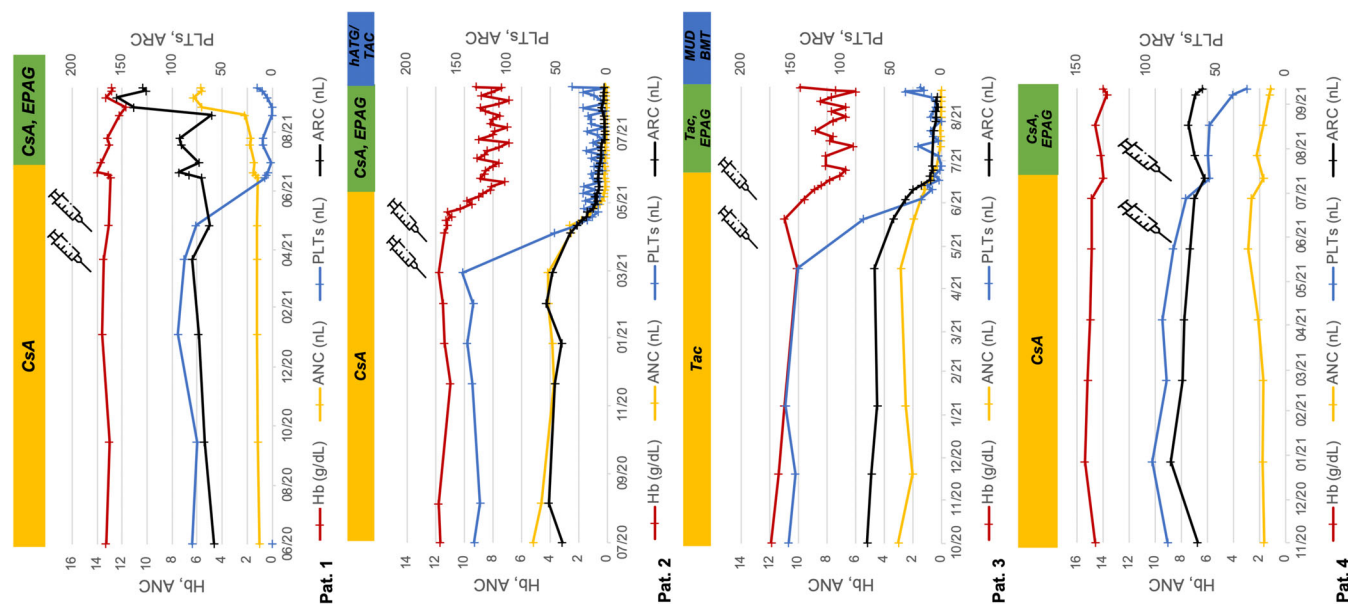Due to the small sample size, statistical analyses were not performed.

3 | RESULTS

Between March 2021 and November 2021, histologic confirmation of relapse of AA in four out of 135 AA patients, of which three patients had opposed vaccination, treated at our department shortly after vaccination against SARS-CoV-2 (3%) (median time after 1st COVID-19 vaccination: 77 days, range 53–113 days) was observed. None of the patients received a vaccination other than Comirnaty® prior to diagnosis of AA relapse and all patients were in stable hematologic remission prior to vaccination (22 months, range 16–60 months). Furthermore, in two other patients, de novo diagnosis of AA was in timed context to COVID-19 vaccination.

3.1 | Temporal-related relapse of AA after SARS-CoV-2 vaccination

Relapse of AA, as previously mentioned, was diagnosed in four adult AA patients (>18 years of age) throughout observation time. The respective characteristics of these patients before COVID-19 vaccination, including the date and the specific vaccine used at that time, in addition to laboratory parameters prior to and post COVID-19 vaccination are listed for each patient in Table 1.

As mentioned, all patients were in stable hematologic remission for AA prior to COVID-19 vaccination, which was further evidenced

TABLE 1 (Continued)

Patient	1	2	3	4
ARC (nl)	62.5	–	67	69
Most recent laboratory parameters post second COVID-19 vaccination				
Days	35	5	6	13
Hb (g/dl)	12.9	11.4	11	14
ANC (nl)	1.14	2.54	1.9	1.7
Platelets (nl)	7	53	78	55
ARC (nl)	70.7	37.1	48	58.3

Abbreviations: AA, aplastic anemia; ARF, acute renal failure; ANC, absolute neutrophil count; ARC, absolute reticulocyte count; BAU, Binding Antibody Units; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COVID-19, coronavirus-induced disease 2019; CR, complete remission; CsA, cyclosporine; EPAG, eltrombopag; FL, follicular lymphoma; FLAER, fluorescein-labeled proaerolysin; Gran, granulocytes; hATG, horse antithymocyte globulin; Hb, hemoglobin; IgG, immunoglobulin G; nSAA, non-severe aplastic anemia; NV, no value; pRBCs, packed red blood cells; PNH, paroxysmal nocturnal hemoglobinuria; rATG, rabbit antithymocyte globulin; severe aplastic anemia; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide phosphate; SARS-CoV-2 S, severe acute respiratory syndrome coronavirus 2 spike protein (S1); TAC, tacrolimus; vSAA, very severe aplastic anemia; yrs., years.

FIGURE 1 Clinical and laboratory courses following COVID-19 vaccination ($N = 4$). ANC, absolute neutrophil count (normal range, 1.7–6.2); ARC, absolute reticulocyte count (normal range, 27–93); ASDCL, naphthol-AS-D-chloroacetate esterase; CsA, cyclosporine; EPAG, eltrombopag; hATG, horse antithymocyte globulin; H&E, hematoxylin and eosin; Hb, hemoglobin (normal range, 13.7–17.2); MUD-BMT, matched unrelated bone marrow transplantation

in two patients (patient 1 and 2) shortly before vaccination was carried out (<7 days). All patients were vaccinated with a mRNA-based vaccine (Comirnaty®) and received their second vaccine dose within the recommended period of three to six weeks[27] (patient 1: 43 days; patient 2: 29 days; patient 3: 42 days; patient 4: 42 days).

In patient 1, transfusion-dependent thrombocytopenia was documented for the first time on day 78 following the first COVID-19 vaccine dose (day 35 after second vaccine dose). Following confirmation of AA relapse (day 86 after first COVID-19 vaccination), eltrombopag (EPAG) in addition to CsA was initiated, resulting in transfusion independence on day 87 of treatment. Regarding the remaining laboratory parameters, the course was stable during the entire presentations at our department.

In patient 2, relapse of AA (vSAA) was confirmed by bone marrow biopsy on day 46 after first dose of COVID-19 vaccine administration (day 16 post second vaccine dose) with evidence of progressive trilinear cytopenia, resulting in transfusion requirement for both, platelets and packed red blood cells (pRBCs). As disease was unresponsive to EPAG/CsA (treatment duration: 111 days), horse ATG (hATG)/CsA was used as salvage therapy. Secondary to acute CsA-induced renal failure, a switch from CsA to tacrolimus (TAC) was further indicated over time.

In patient 3, a sudden and unexpected deterioration of the previously stable laboratory parameters (since Feb. 2019), suggestive for relapse of AA, was observed and closely related to COVID-19 vaccination. In the subsequent bone marrow biopsy, AA relapse was confirmed on day 68 following first COVID-19 vaccine administration and on day 26 after second vaccine dose, respectively. As in patients 1 and 2, EPAG was initiated in this patient. However, due to EPAG/TAC-refractory vSAA (treatment duration: 81 days) with persistence of platelet and pRBC transfusion support in addition to very severe neutropenia, the patient underwent matched unrelated donor (MUD) bone marrow transplantation (BMT) in September 2021. Prior to

BMT, disease course was complicated by atypical pneumonia suggestive for pulmonary aspergillosis in the context of severe neutropenia.

In patient 4, an initial, however, slow decline in platelets with subsequent evidence of neutropenia, suggestive for relapse of AA was observed. On day 113 following first vaccine dose administration, relapse of AA was confirmed. Prior to histologic confirmation of AA relapse, treatment with EPAG was initiated due to a leading decline in platelets and subsequent evidence of severe neutropenia (grade 3).

The clinical and laboratory data following COVID-19 vaccination, including bone marrow histology for each individual patient with confirmed AA relapse are presented in Figures 1 and 2.

3.2 | Anti-SARS-CoV-2 S antibody levels in patients with relapse of aplastic anemia following COVID-19 vaccination

IgG antibodies directed against the SARS-CoV-2 spike protein S1 (BAU/ml) in patients with temporal-related relapse of AA were measured >4 weeks after the first vaccination dose are shown in Table 2 (determination of anti-SARS-CoV-2 S IgG-antibody levels [days] after 2nd vaccination dose: patient 1: 51 days; patient 2: 78 days; patient 3: 33 days; patient 4: 50 days).

3.3 | Temporal-related de novo aplastic anemia after SARS-CoV-2 vaccination

In two female patients de novo, timely related AA after COVID-19 vaccination was observed. Of note, one of the patients suffered from COVID-19 8 months prior to vaccination. Unfortunately, in none of
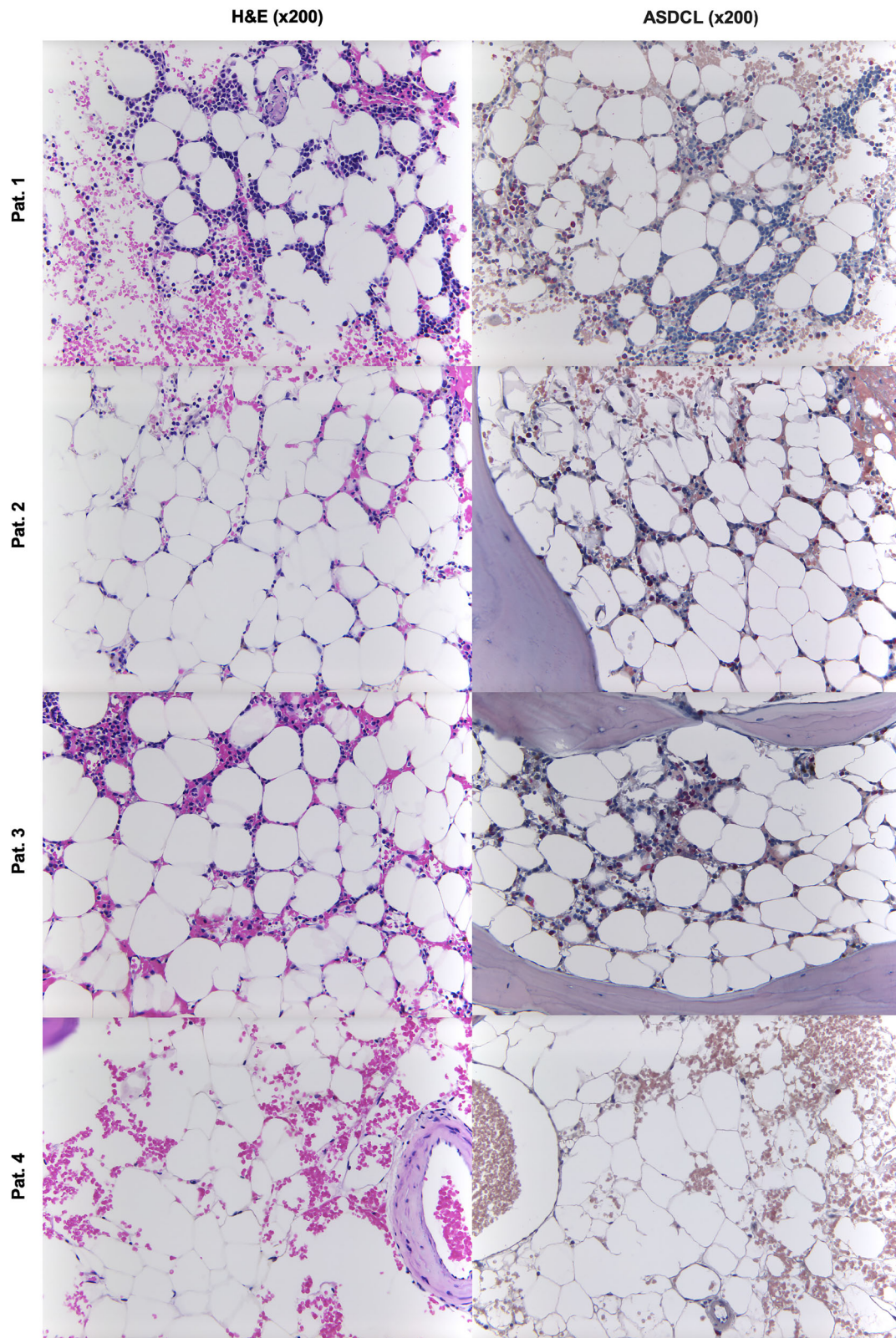
FIGURE 2 Histologic confirmation (stainings: H&E, ASDCL; total magnification ×200) of AA relapse (N = 4). Bone marrow histology. Pat. 1. Hypocellular bone marrow (cellularity <30%) with a left-shifted erythropoiesis (erythropoietic cells partly organized in clusters) and a severely reduced granulo- and megakaryopoiesis. No evidence of myelodysplasia (bone marrow trepanate: 2 cm); Pat. 2. Severely hypocellular bone marrow (cellularity 5%) with a severely reduced granulo- and erythropoiesis and a completely absent megakaryopoiesis. No evidence of myelodysplasia or acute myeloblastic leukemia (bone marrow trepanate: 1.4 cm); Pat. 3. Aplastic bone marrow (cellularity 1%) with no demarceable hematopoiesis (bone marrow trepanate: 1.8 cm); Pat. 4. Completely acellular bone marrow/exclusively fatty marrow with hemorrhages (cellularity 0%) (bone marrow trepanate: 1.4 cm)
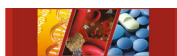
TABLE 2 Anti-SARS-CoV-2 S antibody levels in patients with relapse of AA following COVID-19 vaccination (N = 4)

Patient	1	2	3	4
COVID-19 vaccine	Comirnaty®	Comirnaty®	Comirnaty®	Comirnaty®
First dose (date)	29.03.2021	26.03.2021	28.04.2021	26.05.2021
Second dose (date)	11.05.2021	25.04.2021	09.06.2021	07.07.2021
Anti-SARS-CoV-2 S antibody levels (IgG) (BAU/ml) (days, past first COVID-19 vaccine administration)	>2080 (94)	772 (108)	>2080 (75)	580 (92)

Abbreviations: AA, aplastic anemia; BAU, Binding Antibody Units; COVID-19, coronavirus-induced disease 2019; IgG, immunoglobulin G; SARS-CoV-2 S, severe acute respiratory syndrome coronavirus 2 spike protein (S1).

TABLE 3 Characteristics of patients with de novo AA following COVID-19 vaccination (N = 2)

Patient	4	5
Gender	Female	Female
Relevant past medical history	–	COVID-19 infection (01/2021)
AA grade (age at diagnosis, yrs.)	SAA (77)	vSAA (67)
PNH clone size at diagnosis (Gran., %, FLAER)	1.3	–
COVID-19 vaccine	CoronaVac®	Comirnaty®
First dose (date)	21.04.2021	16.06.2021
Second dose (date)	25.05.2021	–
Diagnosis of AA (date)	30.08.2021	01.09.2021
Diagnosis of AA post COVID-19 vaccination		
First vaccine dose (days)	131	77
Second vaccine dose (days)	97	–
First laboratory parameters post COVID-19 vaccination by the time of presentation at our department		
Hb (g/dl)	8.5	7.7 (transfused)
ANC (nl)	1.3	0.2
Platelets (nl)	10	12 (transfused)
ARC (nl)	–	12.7
Anti-SARS-CoV-2 S antibody levels (Ig G) (BAU/ml) (days, past first COVID-19 vaccine administration)	273 (163)	–
AA-related therapy	hATG/CsA (09/2021)	hATG/CsA (09/2021)

Abbreviations: AA, aplastic anemia; ANC, absolute neutrophil count; ARC, absolute reticulocyte count; BAU, Binding Antibody Units; COVID-19, corona virus-induced disease 2019; CsA, cyclosporine; FLAER, fluorescein-labeled proaerolysin; Gran., granulocytes; hATG, horse antithymocyte globulin; Hb, hemoglobin; Ig G, immunoglobulin G; PNH, paroxysmal nocturnal hemoglobinuria; SAA, severe aplastic anemia; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; vSAA, very severe aplastic anemia; yrs., years.

these patients, laboratory parameters prior to diagnosis of AA were available to the state of file. Patients' laboratory data, including the date and the specific vaccine administrated at that time are presented in Table 3.

Both patients subsequently received IST with hATG/CsA for treatment of AA.

4 | DISCUSSION

Clinical interpretation of our data clearly requires caution, as in none of the patients vaccine-independent relapse of AA or de novo AA can completely be excluded. Neither can SARS-CoV-2-induced AA be excluded in the one patient previously suffering from COVID-19 and diagnosis of de novo AA. However, taking the temporal relationship into account, vaccine-related adverse events can neither be excluded as our observation demonstrates for the first time in literature in a substantial number of patients in stable hematologic remission a risk for relapse of AA in timed context to COVID-19 vaccination.

As previously mentioned, all suspected cases of vaccine-associated AA relapse were reported to the PEI. Based on our observations, a warning was also sent to the German Society of Hematology and Medical Oncology (DGHO),[28] which was published on 27.09.2021.

Remarkable seems to be the fact, that all relapsed patients were vaccinated with the mRNA-based vaccine Comirnaty®. However, whether there is merely an increased risk for disease recurrence after vaccination with Comirnaty® cannot be primarily inferred from our observations. The reason that patients were preferentially vaccinated with Comirnaty® is based on several facts. Following the recommendation of the German Federal Ministry of Health issued on February 2021, patients with AA were classified as high-priority individuals due to an increased risk for a severe or even fatal disease course following SARS-CoV-2 infection. This recommendation was further supported by the DGHO favoring mRNA-based vaccines in these patients due to an improved vaccine response compared to the vector-based vaccine Vaxzevria®.[29–31]

Although we did not perform any functional analyses, a potential explanation for an increased relapse risk in patients with AA despite stable hematologic remission could be related to the enhanced CD8+ T-cell-dependent activation and immune-mediated response of mRNA-based vaccines. Special attention should be drawn in our opinion to mRNA-vaccine (T-cell)-induced T-bet (T-box transcription factor TBX21) transcription factor activation as recently shown by Oberhardt et al.[32] T-bet is critical to T helper
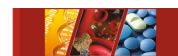
1 (Th1) cell differentiation and is highly expressed in patients with AA. Furthermore, active transcription of the interferon-γ (IFN-γ) gene, resulting in increased IFN-γ levels, is suggested to result from T-bet up-regulation as demonstrated by Solomou et al.[33] Of note, increased levels of both, T-bet and IFN-γ, correlate with disease activity.[33]

This potential mechanism might, therefore, explain the refractoriness to EPAG in three out of our patients, thus favoring BMT, if mRNA vaccine-induced AA relapse is suspected. In patients not suitable for BMT, IST with ATG/CsA, however, might still be an alternative therapeutic option depending age and clinical status of the patient.

In summary, our observations should prompt clinicians to take relapse of AA after vaccination against SARS-CoV-2 as a possible vaccine-related adverse event into account. In addition, careful clinical monitoring and vigilance for signs or symptoms that may indicate relapse of AA (e.g., bleeding complications) following vaccination is recommended.

Prior to booster vaccination, as recently recommend for patients >60 years of age or for moderately and/or severely immunosuppressed patients with an increased risk for a severe disease course, determination of anti-SARS-CoV-2 S antibody levels might further be a useful measure in patients with AA, as an unpredictable immune-mediated, T-cell dependent response has to be avoided. However, when interpreting the measured antibodies, it is important to remember that currently no threshold value for the number of binding antibodies and loss of protection against infection exists.[34] However, further studies are mandatory to investigate the impact of clonal hematopoiesis and the risk of relapse of AA after SARS-CoV-2 vaccination in AA.

AUTHOR CONTRIBUTIONS

AR and FA conceived the study. AR and TS directed the clinical activities. AR, SB, TH, SV, CH, and FA directed the research activities. FA wrote the manuscript. All authors interpreted the data and gave final approval of the manuscript.

CONFLICTS OF INTEREST

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

All data sets generated for this study are included in the article.

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REFERENCES

1. Wang L, Liu H. Pathogenesis of aplastic anemia. *Hematology*. 2019;24(1):559-566.
2. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. *Blood*. 2006;108(8):2509-2519.
3. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*. 2016;172(2):187-207.
4. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020;91(1):157.
5. COVID-19 Vaccines FDA. Accessed September 19, 2021. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines.
6. COVID-19 Vaccines. European Medicines Agency. Accessed September 19, 2021. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines
7. COVID-19-Bone Marrow Failure and PNH Recommendations On behalf of the Severe Aplastic Anemia Working Party, European Group for Blood and Marrow Transplantation (EBMT).
8. Young, N, Robert Brodsky, R, Dunbar, C, Marsh, J & Peffault de Latour R. COVID-19 and Aplastic Anemia: Frequently Asked Questions. Accessed September 19, 2021. https://www.hematology.org/covid-19/covid-19-and-aplastic-anemia
9. von Lilienfeld-Toal, M, Giesen, N, Greinix, H, Hein, A, Hirsch, HH, Langer, F, Na, I.-K, Sandherr, M, Schanz, U, Vehreschild, JJ, Wörmann B. Coronavirus-Infektion (COVID-19) bei Patient*innen mit Blut- und Krebserkrankungen – Onkopedia. Available online: https://www.onkopedia.com/de/onkopedia/guidelines/coronavirus-infektion-covid-19-bei-patient-innen-mit-blut-und-krebserkrankungen/@@guideline/html/index.html (accessed on 19 Sep 2021).
10. Paton C, Mathews L, Groarke EM, et al. COVID-19 infection in patients with severe aplastic anaemia. *Br J Haematol*. 2021;193(5):902-905.
11. Sumbly V, Siddiqui R, Alshamam M, Kurbanova T, Rizzo V. New onset aplastic anemia after a COVID-19 infection: a case report. *Am. J. Med. Case Reports*. 2021;9(9):451-455.
12. Avenoso D, Marsh JCW, Potter V, et al. SARS-CoV-2 infection in aplastic anemia. *Haematologica*. 2022;107(2):541-543.
13. Angelini P, Kavadas F, Sharma N, et al. Aplastic anemia following varicella vaccine. *Pediatr Infect Dis J*. 2009;28(8):746-748.
14. Rauff B, Idrees M, Shah SAR, et al. Hepatitis associated aplastic anemia: a review. *Virol. J*. 2011;8(1):1-6.
15. Viallard JF, Boiron JM, Parrens M, et al. Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol*. 2000;110(1):230-233.
16. Ashok Shenoy K, Shenoy KA, Adhikari MRP, et al. Pancytopenia after recombinant hepatitis b vaccine - an indian case report. *Br. J. Haematol*. 2001;114(4):954-962.
17. Shah C, Lemke S, Singh V, Gentile T. Case reports of aplastic anemia after vaccine administration. *Am J Hematol*. 2004;77(2):204.
18. Donnini I, Scappini B, Guidi S, Longo G, Bosi A. Acquired severe aplastic anemia after H1N1 influenza virus vaccination successfully treated with allogeneic bone marrow transplantation. *Ann Hematol*. 2012;91(3):475-476.
19. Hendry CL, Sivakumaran M, Marsh JCW, Gordon-Smith EC. Relapse of severe aplastic anaemia after influenza immunization. *Br J Haematol*. 2002;119(1):283-284.
20. Ritz C, Meng W, Stanley NL, Baroja ML, Xu C, Yan P, Huang AC, Hausler R, Nicholas P, Fan JM, Lieberman D, Carreno BM, Luning Prak ET, Olson TS, Babushok DV. Postvaccination graft dysfunction/aplastic

anemia relapse with massive clonal expansion of autologous CD8+ lymphocytes. *Blood Adv*. 2020;4(7):1378-1382.

21. Cecchi N, Giannotta JA, Barcellini W, Fattizzo B. A case of severe aplastic anaemia after SARS-CoV-2 vaccination. *Br. J. Haematol*. 2021;196:1334-1336.

22. Sridhara S, Nair R, Stanek M. Severe aplastic anemia after receiving SARS-CoV-2 Moderna mRNA vaccination. *J Hematol*. 2022;11(1):34-39.

23. Tabata S, Hosoi H, Murata S, Takeda S, Mushino T, Sonoki T. Severe aplastic anemia after COVID-19 mRNA vaccination: causality or coincidence? *J Autoimmun*. 2022;126:102782.

24. Schrezenmeier H, Brümmendorf TH, Deeg HJ, Höchsmann B, Machherndl-Spandl S, Panse J, Passweg J, Röth A, Schubert A, Wörmann B. Aplastische Anämie - Onkopedia. Available online: https://www.onkopedia.com/de/onkopedia/guidelines/aplastische-anaemie/@@guideline/html/index.html (accessed on 29 Sep 2021).

25. Bacigalupo A. How I treat acquired aplastic anemia. *Blood*. 2017;129(11):1428-1436.

26. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):208-216.

27. RKI - Empfehlungen der STIKO - Mitteilung der STIKO zur COVID-19-Impfung: Impfabstand und heterologes Impfschema nach Erstimpfung mit Vaxzevria (1.7.2021). Available online: https://www.rki.de/DE/Content/Kommissionen/STIKO/Empfehlungen/PM_2021-07-01.html (accessed on 29 Sep 2021).

28. Coronavirus-Infektion (COVID-19) bei Patient*innen mit Blut- und Krebserkrankungen - Onkopedia. Available online: https://www.onkopedia.com/de/onkopedia/archive/guidelines/coronavirus-infektion-covid-19-bei-patient-innen-mit-blut-und-krebserkrankungen/version-19012022T101518/@@guideline/html/index.html (accessed on 03 Oct 2021).

29. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19. *Vaccine*. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577

30. Baden LR, El SHM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2. *Vaccine*. 2020;384(5):403-416. doi:10.1056/NEJMoa2035389

31. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111.

32. Oberhardt V, Luxenburger H, Kemming J, et al. Rapid and stable mobilization of CD8+ T cells by SARS-CoV-2 mRNA vaccine. *Nature*. 2021;597(7875):268-273.

33. Solomou EE, Keyvanfar K, Young NS. T-bet, a Th1 transcription factor, is up-regulated in T cells from patients with aplastic anemia. 2006, 2006;107(10):3983-3991.

34. Krammer F. A correlate of protection for SARS-CoV-2 vaccines is urgently needed. *Nat Med*. 2021;27(7):1147-1148.