Case report

BF and RP contributed equally

Aplastic anemia after SARS-CoV-2 infection or vaccines: case series and literature review

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INTRODUCTION

There is increasing interest in the relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or vaccines against this infection and the development/exacerbation of autoimmune diseases, including autoimmune cytopenias and complement-mediated diseases. Exacerbations of autoimmune hemolytic anemia and immune thrombocytopenic purpura secondary to coronavirus disease 2019 (COVID-19) and vaccines have been reported frequently, while the association with aplastic anemia (AA) or pure red cell aplasia (PRCA) is rarer[1,2]. AA is a very rare life-threatening bone marrow failure syndrome with an incidence of 2-4 cases/million inhabitants per year, characterized by pancytopenia with immune-mediated loss of hematopoietic stem cells[3]. The trigger of the autoimmune activation leading to AA is often unknown; however, several reports highlight an association with infections (particularly hepatitis viruses), and vaccinations, such as varicella, hepatitis B and influenza vaccinations. PRCA is marked by a reduction of red blood cells and absence of marrow erythroid precursors, due to parvovirus infection, or to autoimmunity triggered by infections, drugs, thymoma, etc.[3-6]

Here, we report a single center experience of AA cases diagnosed after the administration of a SARS-CoV-2 vaccine, focusing on the clinical severity, peculiar bone marrow features, and treatment outcome. Moreover, we provide a review of available literature regarding the development/exacerbation of AA in the SARS-CoV-2 era.

MATERIALS AND METHODS

Patients diagnosed with AA at a single tertiary hematology center in Milan, Italy from March 2020 to March 2022 (i.e., during the main waves of the COVID-19 pandemic and subsequent vaccination campaign) were included in the analysis. Clinical and laboratory data, treatment, and outcome information were collected retrospectively. The timing in relation to the SARS-CoV-2 infection or vaccine, as well as vaccine type, were also recorded. The study was conducted according to the Declaration of Helsinki and patients gave informed consent. The study was approved by the local Ethical Committee.

Bone marrow (BM) trephine biopsies from six patients were reviewed by an expert hemopathologist. Histological parameters were assessed on Giemsa stain and with a panel of antibodies for the following antigens: CD8 (clone C8, Dako Agilent) [Agilent, Santa Clara, CA, USA], C3 (polyclonal, Merck [Rahway, NJ, USA]), C4d (polyclonal, Cell Marque [Rocklin, CA, USA]), IgM (polyclonal, Dako Agilent), IgG (polyclonal, Dako Agilent), cleaved-Caspase_3 (Asp175 clone, Cell Signaling [Danvers, MA, USA]) and SARS-CoV-2

Spike Protein S1 (clone HL6, Thermo Fisher [Waltham, MA, USA]). Results were compared with those from five patients who had developed AA before the COVID-19 pandemic.

A review of the literature on AA and PRCA occurring after SARS-CoV-2 infection or vaccination was performed by searching for indexed articles and published abstracts up to September 2022 in MEDLINE via PubMed and the National Library of Medicine.

CASE SERIES

A total of eight cases of AA were included, six severe (SAA) and two non-severe (NSAA), with a median age of 61.75 years (range, 40-83), five males and three females. **Table I**

Table I - *Aplastic anemia developing or relapsing after SARS-CoV-2 vaccination/infection*

Case	AA grade	Date of diagnosis	Age (years)	Sex	Hb (g/L)	PLT (x 10⁹/L)	ANC (x 10⁹/L)	EPO (U/L)	Ret (x 10⁹/L)	Cytogenetic	Vaccine/infection	Time between infection/vaccination and AA	AA treatment outcome
1	SAA	21st Sep 2021	40	F	47	40	0.89	1,052	10.4	Normal	Vaccine (Moderna) 2nd dose in Aug 2021	10 days after 2nd dose	Steroid® PR CYA and EPAG® CR Alive
2	SAA	5th Apr 2021	72	F	103	68	0.46	408	4.4	Normal	Vaccine (NA type) 1st dose in Feb 2021	60 days	Steroid (STOP)® NR CYA® NR Alive
3	NSAA	6th Oct 2021	43	M	95	17	1.4	543	8	Trisomy of chromosome 6 (1 metaphase) and Y deletion (1 metaphase)	Infection in Nov 2020 Vaccine (Pfizer) 1st dose in Apr 2021	210 days after infection 60 days after 1st dose	Steroid and CYA® NR EPAG® PR Alive
4	NSAA	2nd Mar 2022	83	M	85	5	0.98	NA	4.3	Normal	Vaccine (Pfizer) 2 doses in Apr 2021, 3rd dose in Nov 2021	150 days after 2nd dose	Steroid, CYA and EPAG (+ EPO by nephrologist)® NR Alive *(Danazol is under evaluation)*
5	SAA	24th Feb 2022	72	M	91	6	1.1	571	150	Normal	Vaccine (Moderna) 3rd dose in Dec 2021	90 days after 3rd dose	Steroid, CYA and rATG® NR EPAG® NR Death for complications
6	SAA	12th Apr 2021	77	M	112	3	0.49	NA	NA	Normal	Vaccine (Pfizer) 1st and 2nd doses in Feb/Mar 2021	Some months	CYA and rATG® PR Alive
7	SAA	12th Nov 2021	49	M	116	3	1.9	NA	NA	NA	Vaccine (Pfizer) 1st and 2nd dose in Feb/Mar 2021	Some months	CYA and rATG® CR Alive
8	SAA	08th Nov 2021	58	F	39	0	0.37	771	2.9	Normal	Vaccine (NA type) 2nd dose in Jun 2021	Concomitant	CYA and rATG® NR EPAG® NR Danazol ongoing *HSCT is under evaluation* Alive

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AA: aplastic anemia; Hb: hemoglobin; PLT: platelet count; ANC: absolute neutrophil count; EPO: erythropoietin; Ret: reticulocyte count; F: female; M: male; NA: not available; PR: partial response; CYA: cyclosporine A; EPAG: eltrombopag; CR: complete response; NR: no response; rATG: recombinant antithrombocyte globulin; HSCT: hematopoietic stem cell transplantation. Pfizer, New York, NY, Usa; Moderna, Cambridge; MSA, USA.

summarizes the patients' clinical and laboratory features. All cases were diagnosed *de novo* at a median of 2.29 months after the last dose of anti-SARS-CoV-2 vaccine. Three patients were diagnosed after the first dose, three after a second dose, and two after a third dose. Notably, one patient had also experienced SARS-CoV-2 infection 6 months before vaccination. Patients were treated with anti-thymocyte globulin (ATG) plus cyclosporine (CYA) in four cases (all SAA), CYA alone in three cases (2 SAA and 1 NSAA), and CYA plus eltrombopag (EPAG) in one case (NSAA). At 6 months of treatment, response rates were: 75% with ATG plus CYA, and 66% with CYA alone. The addition of EPAG induced a hematological improvement in all the four non-responding patients after a median of 2.5 months. Contrarily, the patient treated upfront with CYA in combination with EPAG did not respond. At the last follow-up, four patients were maintaining a stable hematological response on treatment, three patients had required a further line of therapy (hematopoietic stem cell transplantation, EPAG, danazol), and one had died.

BONE MARROW EVALUATION

Bone marrow trephines (**Figure 1**) displayed features of hypoplasia or aplasia, with unremarkable morphological dysplasia and no increase in blasts. As expected, an accompanying infiltrate composed of (mostly CD8$^+$) T cells was present in all cases. Variable, but mostly abundant anti-IgM and anti-IgG immunoreactivity was observed in a serous pattern (i.e., extracellular deposits within vessel lumina) and, in four cases, also with enhancement on red blood cell membranes. A serous pattern of immunoreactivity was also detected for C3 and C4d in all cases but one. With the limits of the sensitivity of immunohistochemistry on paraffin-embedded tissue, no deposits of C3, C4d, IgM or IgG could be reliably identified on nucleated cells. In no case was integration of spike protein observed. Anti-cleaved caspase-3 evaluation showed no remarkable signs of apoptosis in the study cohort.

The comparison with the control group of AA patients diagnosed before the SARS-CoV-2 pandemic showed an overlapping pattern, although with globally lower burdens of deposition, as semi-quantitatively assessed by the intensity and distribution of immunoreactivity (*Online Supplementary Content*, **Table SI**).

REVIEW OF THE LITERATURE

Table II summarizes available clinical reports of AA developing after COVID-19 or SARS-CoV-2 vaccines. Regarding the former, Avenoso *et al.* reported three cases of SAA diagnosed a few weeks after SARS-CoV-2 infection who required treatment with immunosuppressive therapy or hematopoietic stem cell transplantation and recovered[5]. Additionally, Lee *et al.* described five cases of new-onset SAA and one case of PRCA. Patients were mainly females (4/6) with a median age of 28 years (range, 22-76) and
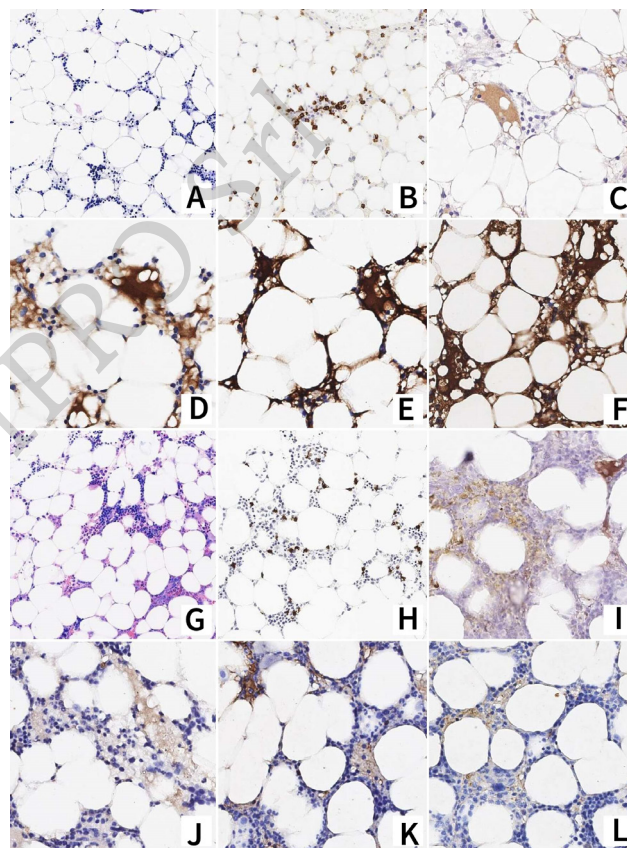

Figure 1 - Immunohistochemistry studies on bone marrow samples from a patient with aplastic anemia and a control case with bone marrow hypoplasia

Representative panel (**A-F**) of a post-vaccine aplastic anemia (AA) case, depicting a severely hypocellular bone marrow (**A**. Giemsa, 200x) with a CD8$^+$ T-cell infiltrate (**B**. 200x), a moderate-high burden of serous C3 (**C**. 400x) and C4d (**D**. 400x) deposits as well as intense extracellular deposits of IgM (**E**. 400x) and IgG (**F**. 400x). Panel (**G-L**) depicting a control case with bone marrow hypoplasia (**G**. Giemsa, 200x) and a moderate amount of CD8$^+$ T cells (**H**. 200x); complement fractions C3 (**I**. 400x) and C4d (**J**. 400x) show a lower burden of reactivity, in a serous pattern, but with enhancement on the red blood cell membranes; a similar profile is observed for IgM (**K**. 400x) and IgG (**L**. 400x), the former featuring a more intense reactivity.

Table II - Aplastic anemia developing or relapsing after SARS-CoV-2 infection and vaccination

Study type	AA grade	De novo/Relapse	Patients	Sex	N	Vaccine/infection	Time between infection/vaccination and AA diagnosis	COVID-19/AA treatment Outcome	First author, year,[ref]
Case report	SAA	De novo	Child (6 y)	F	1	Infection	Concomitant	Convalescent plasma® pancytopenia persistence after SARS-CoV-2 clearance, only transfusion support	Figlerowicz et al. 2020,[8]
Case series	SAA	De novo	Adults	/	3	Infection	A few weeks (not specified)	CYA and HSCT (only aggregated data reported) with CR	Avenoso et al. 2022,[5]
Case series	SAA SAA PRCA SAA SAA SAA	De novo	Adult (22 y) Adult (69 y) Adult (72 y) Adult (21 y) Adult (69 y) Adult (28 y)	F F M M F F	6	Infection	10 days 2 days 120 days 7 days 150 days 90 days 210 days	HSCT® CR; CYA, hATG and EPAG® PR CYA/TAC® CR CYA, hATG, and EPAG® CR CYA, hATG and EPAG® NA CYA, hATG and EPAG® PR	Lee NCJ et al. 2022,[7]
Case report	SAA	De novo	Adult (76 y)	M	1	Vaccine (Pfizer-BioNTech mRNA vaccine)	days after the 2nd dose	Steroid® NR; CYA + rATG® CR	Cecchi et al. 2021,[S1]
Case series	NSAA NSAA SAA VSAA (all patients had prior AA and received CYA, hATG, EPAG)	Relapse	Adult (19 y) Adult (82 y) Adult (47 y) Adult (52 y)	M	4	Vaccine (Pfizer-BioNTech mRNA vaccine)	74 days after 1st dose, 35 days after 2nd dose 46 days after 1st dose, 16 days after 2nd dose 68 days after 1st dose, 26 days after 2nd dose 113 days after 1st dose	CYA + EPAG® CR CYA + EPAG® NR; hATG + CYA® improvement but toxicities; TAC® NA EPAG + TAC →NA; HSCT® NR EPAG® NA	Röth et al., 2022,[9]
Case reports	SAA VSAA	De novo	NA	F	2	Vaccine (CoronaVac) Vaccine (Pfizer-BioNTech mRNA vaccine)	90 days after 3rd dose 90 days after 1st dose	hATG/CYA® NA	Röth et al., 2022,[9]
Case report	VSAA	De novo	Adult (56 y)	M	1	Vaccine (Pfizer-BioNTech mRNA vaccine)	21 days after 1st dose, 4 days after 2nd dose	G-CSF® NR; CYA and EPAG® NR HSCT® CR	Tabata et al., 2022,[S2]
Case report	SAA	De novo	Adult (60 y)	M	1	Vaccine (Moderna)	14 days after 2nd dose	CYA, ATG, EPAG and steroids® Death from heart attack	Sridhara et al., 2022[S3]
Case report	VSAA	De novo	Adult (53 y)	M	1	Vaccine (Moderna)	60 days after 2nd dose	CYA, ATG, EPAG® CR	Woo S et al., 2022,[S4]
Case report	NA	De novo	Adolescent (16 y)	F	1	Vaccine (recombinant hepatitis B)	21 days after 3rd dose	G-CSF and steroids® CR	Viallard et al., 2000,[S5]
Case report	NA	De novo	Adolescent (16 y)	F	1	Vaccine (recombinant hepatitis B)	10 days after 3rd dose	Steroids® CR	Shenoy et al., 2001,[S6]

Table II - *Aplastic anemia developing or relapsing after SARS-CoV-2 infection and vaccination (continued from previous page)*

Study type	De novo/Relapse	AA grade	Patients	Sex	N	Vaccine/infection	Time between infection/vaccination and AA diagnosis	COVID-19/AA treatment Outcome	First author, year, [ref]
Case report	Relapse	SAA	Adult (60 y)	F	1	Vaccine (influenza Fluvirin; Medeva)	7 days	Steroids and CYA® CR	Hendry et al. 2002,[S7]
Case reports	De novo	NA	Adults (25 y and 19 y)	M	2	Vaccine (hepatitis B, boost) Vaccine (anthrax)	7 days / 30 days	HSCT® NA / HSCT® NA	Shah et al., 2004,[S8]
Case report	De novo	SAA	Child (17 months)	F	1	VZVAC (VARIVAX III, Merck Frosst)	23 days	No treatment® improvement	Angelini et al., 2009,[S9]
Case report	De novo	SAA	Adult (25 y)	M	1	H1N1 influenza virus vaccine	A few days	HSCT® CR	Donnini et al., 2012,[S10]
Case report	Relapse	SAA (patient for prior SAA underwent HSCT)	Adult (31 y)	M	1	Concurrent pneumococcal conjugate and inactivated influenza vaccines	7 days after vaccine (6 months after HSCT)	Increase CYA, DLI® Improvement in the percentage of donor chimerism	Ritz et al., 2022,[S12]

References from s1 to s9 in Supplementary Content.
Coronavaq (Sinovac Biotech, Beijing, China); Pfizer–BioNTech mRNA vaccine (Pfizer, New York, NY, Usa); Spikevax (Moderna, Cambridge; MSA, USA). Medeva, New Delhi, India; Merck, Rahway, NJ, USA. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; AA: aplastic anemia; y: years; SAA: severe aplastic anemia; PCRA: pre red cell aplasia; F: female; M: male; CYA: cyclosporine A; HSCT: hematopoietic stem cell transplantation; CR: complete response; hATG: human antithrombocyte globulin; EPAG: eltrombopag; rATG: recombinant antithrombocyte globulin; PR: partial response; TAC: tacrolimus; NA: not available; NSAA: non-severe aplastic anemia; VSAA: very severe aplastic anemia; NR: no response; G-CSF: granulocyte colony-stimulating factor; DLI: donor lymphocyte infusion.

developed SAA/PRCA at a median of 10 days (2-210) after a positive nasopharyngeal swab. All patients required treatment with CYA plus ATG and EPAG (n=4), CYA plus tacrolimus (n=1, PRCA), or hematopoietic stem cell transplantation (n=1). All but one responded. Interestingly, two patients had bone marrow trephine biopsied that had been stained for spike protein by immunohistochemistry with negative results. One SAA patient developed fully hemolytic paroxysmal nocturnal hemoglobinuria and was started on eculizumab[7]. Finally, Figlerowicz *et al.* reported the case of a 6-year-old girl who received a diagnosis of AA concomitantly with severe COVID-19 treated with convalescent plasma transfusion; SAA was managed with transfusions only, and cytopenias progressively recovered after resolution of the COVID-19[8].

Regarding AA after SARS-CoV-2 vaccines, a total of ten patients have been described (**Table II**): seven after a Pfizer vaccine, two after a Moderna vaccine, and one after a CoronaVac vaccine. The median age of the affected patients was 56 years (range, 17 months - 60 years); eight were male and two were female. Eight had SAA and two had NSAA; six were *de novo* cases and four were relapses. The four patients with relapsed AA belonged to a cohort of 135 AA patients from the German group[9], and all occurred after mRNA-vaccine (Comirnaty®). The AA was diagnosed at a median of 48 days (range, 14-113) after the last dose of SARS-CoV-2 vaccine. Two patients developed SAA after the first dose, seven after the second dose, and one after a third dose. The patients were treated with ATG plus CYA (n=3, SAA), CYA plus EPAG (n=3, NSAA), CYA plus ATG and EPAG (n=2, SAA), EPAG alone (n=1), and EPAG plus tacrolimus (n=1). One of three patients responded to ATG plus CYA, one of three to CYA plus EPAG (the 2 non-responders further received ATG), one of two to CYA plus ATG and EPAG; response data were not available for four patients.

Regarding AA secondary to other vaccines (**Table II**), a total of eight patients (5 adults and 3 children) have been reported (5 after recombinant hepatitis B vaccines, 2 after influenza vaccines, 1 after varicella-zoster vaccine concomitant with a pneumococcus vaccine). Four patients had SAA and four cases were not graded. Six had *de novo* AA and two had relapses (1 after hematopoietic stem cell transplantation). AA developed at a median of 14 days after the last dose of vaccine. Six patients developed AA after

the first dose, and two after a third dose. The patients were treated with steroids only (n=3, plus granulocyte colony-stimulating factor in 1 case), steroids plus CYA (n=1) all with response, and watch-and-wait with spontaneous improvement in one case. Three patients underwent hematopoietic stem cell transplantation.

DISCUSSION

The SARS-CoV-2 pandemic increased our awareness about post-infectious and post-vaccine complications, including *de novo* or relapsed autoimmune cytopenias. While "peripheral" immune-mediated cytopenias, such as immune thrombocytopenia purpura and autoimmune hemolytic anemia, were reported more frequently, only a few case reports/series of AA have been described; these were mainly *de novo* cases occurring after SARS-CoV-2 vaccine (**Table II**). In our series, the severity and response patterns seem similar to those of primary (idiopathic) AA (**Table II**)[3,10]: patients mainly developed SAA which responded to immunosuppressive treatment plus EPAG in about 70% of cases. It is not possible to establish a definite causative link between SARS-CoV-2 infection/vaccines and the development of AA in our series (**Table I**) or in those collected by others (**Table II**), although the temporal association may suggest a relationship. However, the wide range of time elapsed between SARS-CoV-2 infection or vaccination and the diagnosis of AA (from 2 days to more than 3 months) does not allow clearcut conclusion. An association might also be hypothesized basing on the nearly 2-fold increase of AA frequency during the last 2 years (8 patients) compared to the previous 30 years (42 patients) at our center.

Concerning physiopathology, several possible mechanisms may concur, including overactivation of humoral and cellular immunity, epitope spreading, imbalance of suppressor/regulator T- and B-cell subpopulations, and molecular mimicry[11-14].

Concerning the last possibility, SARS-CoV-2 and mRNA vaccines lead to spreading of the spike protein which has a high level of homology with several human epitopes, including hematopoietic ones[11-14]. It has been proposed that SARS-CoV-2 may directly affect bone marrow precursors, and that integrated spike protein may be found in the latter leading to

post-COVID-19 cytopenias[14]. However, in our series (**Table I**), and in that by Lee *et al.*, bone marrow samples were negative for spike protein while a classical CD8+ T-cell infiltrate was documented[8]. Interestingly, we observed abundant anti-IgM, anti-IgG, anti-C3, and anti-C4d immunoreactivity within the bone marrow of AA patients. This pattern was also recognized in AA patients diagnosed before the SARS-CoV-2 pandemic, although with globally lower burdens of deposition. This may suggest that AA developing after a SARS-CoV-2 vaccine may result from an aberrant immunological storm with cellular (CD8+ T), humoral (IgG and IgM), and complement activation leading to a less specific attack of blood cells and precursors, although further investigation is needed.

In conclusion, there is no clear evidence that either SARS-CoV-2 infection or the respective vaccine directly causes AA, which remains a rare event. However, the broad immune activation deriving from triggers such as infections and vaccines may contribute to the pathogenesis of autoimmune diseases and deserves further studies.

AUTHORS CONTRIBUTIONS

BF, RP, and WB conceived the study and wrote the article. GAC performed bone marrow evaluations and wrote the article. All Authors followed patients, collected data, and revised the article for important intellectual content.

The Authors declare no conflicts of interest.

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ONLINE SUPPLEMENTARY CONTENT

Table SI - *Patterns of complement fractions 3 and 4 (C3 and C4d), immunoglobulins (Ig) M and IgG, and caspase deposition in the bone marrow of aplastic patients diagnosed after SARS-CoV-2 pandemic (study group) and in those diagnosed before (control group)*

ID	C3	C4d	IgM	IgG	Caspase	Morphology
Study group						
1	2, serous	2, serous	2, serous	2, serous	0	Hypoplastic (20%); no dysplasia; initial regeneration of erythroid colonies
2	0	0	3, serous and RBC	3, serous and RBC	0	Hypoplastic (10%); white blood cell aplasia
3	1, serous	2, serous	3, serous and RBC	1, serous and RBC	0	Aplastic (5%); no dysplasia
4	1, serous	1, serous	3, serous	3, serous and RBC	0	Aplastic (5%); no dysplasia
5	2, serous	2, serous	2, serous	2, serous	0	30%, regenerative; no dysplasia
6	2, serous	2, serous	2, serous	3, serous and RBC	0	Aplastic (5%); no dysplasia
Control group						
1	1, serous	1, serous	1, serous	1, serous	1, focal	Hypoplastic (15%); no dysplasia; initial regeneration of erythroid colonies
2	0	0	2, serous	2, serous	0	Hypoplastic (15%); no dysplasia
3	2, serous and RBC	1, RBC	2, serous and RBC	1, serous and RBC	1, precursor + RBC	Hypoplastic (20%); no dysplasia
4	1, RBC	1, RBC	3, serous and RBC	3, serous and RBC	0	Aplastic (<5%)
5	2, serous	1, serous	2, serous and RBC	1, serous and RBC	0	Hypoplastic (10%); no dysplasia

Burden: 1 = low, mostly weak and focal; 2 = intermediate, diffuse, mostly with weak to moderate intensity; 3 = high, mostly diffuse and intense.
Distribution of reactivity: serous = extracellular, best highlighted within vessel lumina; RBC: red blood cells; precursor = nucleated precursors.

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