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CASE REPORT

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Rituximab-induced acute lympholysis and pancytopenia after COVID-19 vaccination

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Abstract

Rituximab and COVID-19 vaccine can cause massive hyperacute depletion of B cells and plasma cells, as well as subsequent cytokine release syndrome, coagulopathy, and pancytopenia. These effects differ from the adverse effects that have been reported for rituximab, and new guidelines regarding the timing of rituximab infusion and vaccination are urgently needed.

KEYWORDS

COVID-19 vaccine, lympholysis, pancytopenia, rituximab

1 | INTRODUCTION

COVID-19 vaccines from Pfizer-BioNTech and Moderna are being implemented rapidly worldwide. Current guidelines or recommendations from multiple institutes and organizations do not adequately acknowledge the potential acute consequences in patients receiving both rituximab and COVID-19 vaccination, and the appropriate timing between rituximab infusion and vaccination has not been established. In this brief report, we report a case of rituximab-induced lympholysis and pancytopenia in a patient who received the second dose of Moderna COVID-19 vaccine 10 days before rituximab infusion. Rituximab not only induced the depletion of CD20+ B cells and plasma cells, but also caused iatrogenic cytokine release syndrome, coagulopathy, and pancytopenia through a subsequent cascade of events. These observations highlight the need for increased cautions when considering both anti-CD20 therapy and COVID-19 vaccination for the same patient and the urgent need to update current guidelines. New guidelines or recommendations regarding COVID-19 vaccination in patients who need anti-CD20 therapies are proposed.

In December 2020, COVID-19 vaccines from Pfizer-BioNTech and Moderna were authorized for emergency use in the United States and are rapidly being implemented in other countries around the world. Many questions have arisen about the safety of vaccination in patients with malignancy, especially in those immunocompromised either from the diseases or their respective treatments. Multiple institutes and organizations have issued recommendations or guidelines on COVID-19 vaccination in cancer patients. COVID-19 Vaccine Interim Guidelines for Cancer Patients (Version 4, February 11, 2021) by Memorial Sloan Kettering Cancer Center (MSKCC)[1] recommend that systemic induction therapy, including anti-CD20 antibodies, for newly diagnosed disease should in general not be delayed for vaccination. Recommendations of the NCCN COVID-19 Vaccination Advisory Committee (Version 2.0, March 10, 2021) by The National Comprehensive Cancer Network (NCCN)[2] do not comment on anti-CD20 therapy when considering COVID-19 vaccine administration.

Anti-CD20 antibody therapies including rituximab, obinutuzumab, ofatumumab, ocrelizumab, tositumomab, and ibritumomab tiuxetan exert cytolytic effects when binding to the CD20 molecules on B-lymphocytes. This anti-tumor activity is attributed to various mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis.[3] Rituximab is a component of standard of care for hematologic B-cell malignancies, including chronic lymphocytic leukemia, diffuse large B-cell lymphoma, and lymphoplasmacytic lymphoma.

Rituximab has been reported to cause acute infusion reactions,[4] late-onset neutropenia,[5] and hepatitis B virus reactivation.[6] Rituximab also reportedly decreases the efficacy of various inactivated vaccines including the pneumococcal,[7] *Haemophilus influenzae* type B (Hib),[7] and influenza vaccines[8] due to the depletion of CD20+ B cells[9] necessary to mount the humoral immune response after vaccination. Administration of live viral vaccines is not recommended in patients on rituximab therapy since the safety has not been established.

No acute events associated with rituximab infusion and recent vaccination, particularly the COVID-19 vaccine, have been described. Here, we report a case of rituximab-induced lympholysis and pancytopenia in a patient who received the second dose of Moderna COVID-19 vaccine 10 days prior to rituximab infusion, highlighting the need for increased caution when considering anti-CD20 therapy with COVID-19 vaccination in cancer patients and the urgent need to update current guidelines.

2 | CASE REPORT

A 71-year-old male veteran was diagnosed with B-cell lymphoplasmacytic lymphoma a.k.a. Waldenstrom's macroglobulinemia (WM) by bone marrow biopsy (BMB) on March 23, 2011. He had been asymptomatic and under observation until he had worsening anemia and thrombocytopenia in June 2014. Repeat BMB showed >80% involvement of the bone marrow by WM. Weekly 375 mg/m^2 intravenous (IV) rituximab for a total of four doses started on August 4, 2014, resulted in excellent responses. Maintenance rituximab weekly ×4 every 6 months was given for 2 years until June 29, 2016, without any complications (Figure 1). Patient was found to have worsening anemia and thrombocytopenia on January 29, 2021. BMB again confirmed recurrent WM with approximately 75% involvement of bone marrow. Positron emission tomography-computed tomography (PET/CT) on February 10, 2021, also showed diffuse lymphadenopathy. The treatment plan was to reinitiate rituximab weekly ×4 followed by maintenance rituximab every 6 months or every year. Scheduled prior to the confirmation of the WM relapse, patient received his first dose of Moderna COVID-19 vaccine on January 29 and the second dose on February 26, 2021.

Patient presented to our infusion center for the first dose of 375 mg/m^2 IV rituximab on March 8, 2021 (Figure 1). Approximately 70 min into infusion, patient reported feeling cold and was shivering. Rituximab infusion was paused, and normal saline was started. His vital signs were stable. Blanket warmer was placed on patient. He stopped shivering and reported symptomatic improvement within 5 min. Approximately 10 min later, rituximab was restarted at previously tolerated rate of 200 mg/h and then increased by 50 mg/h every 30 min. Patient had no other symptoms for the remainder of infusion and tolerated well up to the maximal rate of 400 mg/h.

Patient's family reported that after returning home, he developed a fever up to 39.9°C (103.8°F), chills, disorientation, confusion, and nausea without emesis. He did not have headache, vision changes, rash, tinnitus, dyspnea, cough, chest pain, abdominal pain, or diarrhea. He denied previous reactions of this nature when receiving rituximab infusions in the past. Patient was immediately brought to our emergency room where he was found mildly hypotensive (blood pressure 97/55 mmHg), but not tachycardic (maximum heart rate 95 beats/min) and not febrile anymore. Compared to the laboratory results before the rituximab infusion, his hemoglobin decreased from 11.5 to 9.3 g/dl, white blood cells decreased from 4.7 × 10^3/μl to 1.0 × 10^3/μl, platelet counts decreased from 84 × 10^3/μl to 26 × 10^3/μl, absolute neutrophil counts decreased from 2.36 × 10^3/μl to 0.85 × 10^3/μl, and absolute lymphocyte counts decreased from 1.93 × 10^3/μl to 0.15 × 10^3/μl (Table 1). Peripheral blood smear showed pancytopenia with marked leukopenia secondary to moderate neutropenia and marked lymphocytopenia (Figure 2A). Neutropenic fever

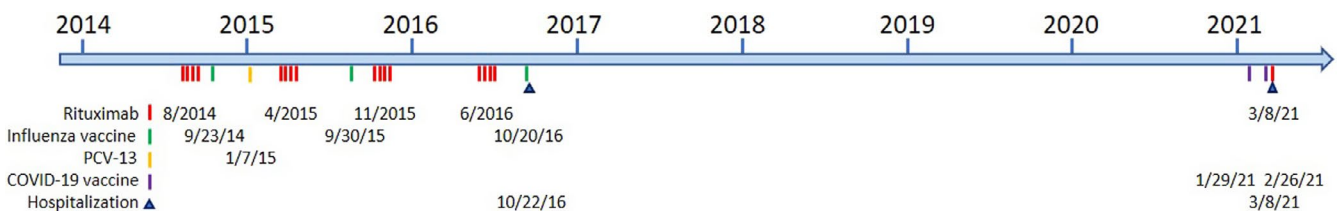

FIGURE 1 2014–2021 time course of rituximab treatments, vaccinations, and hospitalizations. PCV-13, Prevnar 13® pneumococcal 13-valent conjugate vaccine

TABLE 1 Main laboratory data during the clinical course

	Pre-infusion	Day 1	Day 2	Day 3	Day 4	Day 8	Day 22	Day 53	Reference range
White blood cell (x10^3/μl)	4.7	1	1.8	1.7	2	3.5	3.8	5.2	4.0–11.0
Hemoglobin (g/dl)	11.5	9.3	8.2	8.3	8	9.9	10.4	12.7	14.0–17.0
Platelet (x10^3/μl)	84	26	28	30	33	59	76	178	150–400
Neutrophil (x10^3/μl)	2.36	0.85	1.21	1.09	1.52	1.46	1.53	2.55	1.44–7.26
Lymphocyte (x10^3/μl)	1.93	0.15	0.58	0.57	0.52	1.86	1.80	1.97	0.96–4.84
Peripheral blood flow cytometry: % of absolute lymphocyte counts									
T cell				98.7%			90.1%	85.0%	
CD4:CD8 ratio				6.1			2.3	1.9	
NK cell				0.9%			8.4%	12.2%	
B cell				0%			0%	0%	
Plasma cell				0%			0%	0%	
Serum complement component 3 (mg/dl)				81					82–185
Serum complement component 4 (mg/dl)				9					15–53
Serum interleukin-6 (pg/ml)				18.93					≤5.00
Serum interleukin-2 receptor alpha chain (pg/ml)				21,822					532–1891

Note: Day 1 = March 8, 2021.

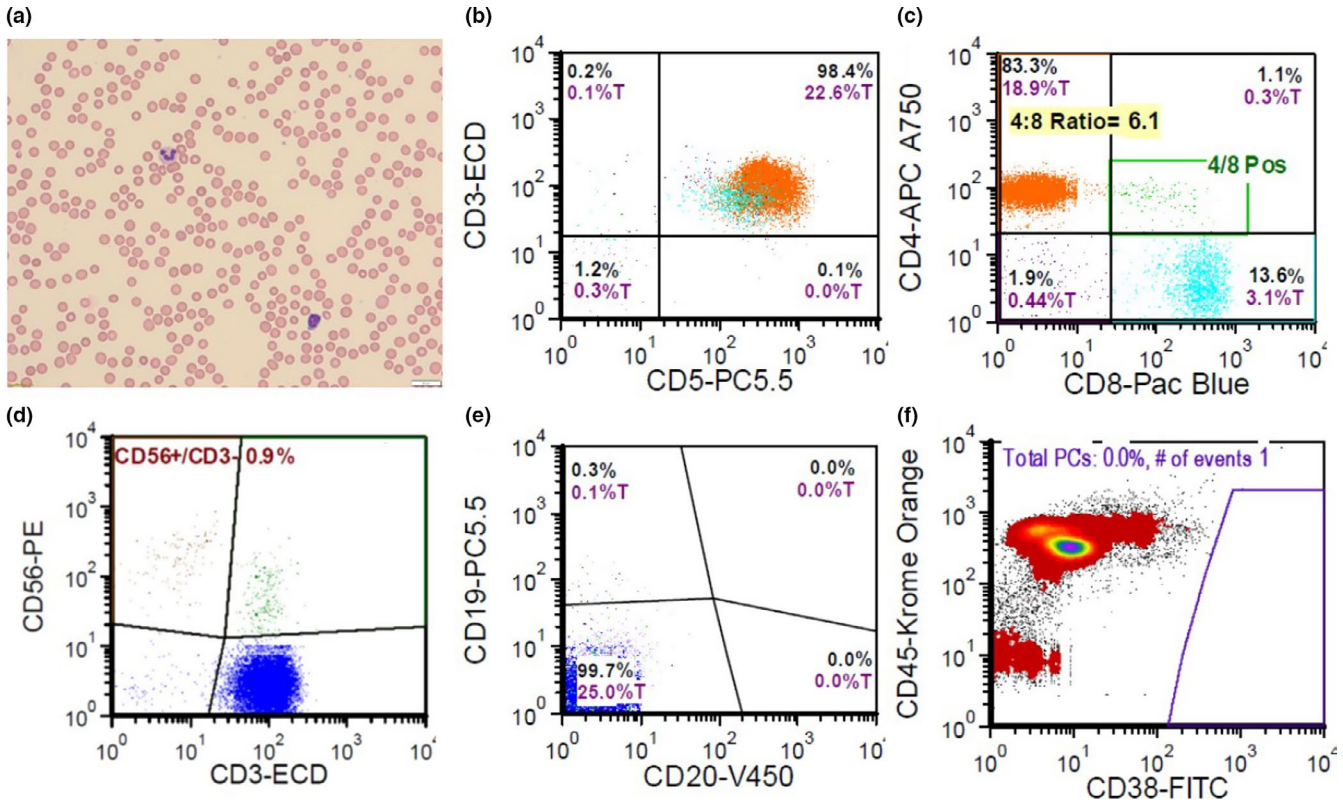

FIGURE 2 Pancytopenia and the depletion of B cells and plasma cells but not T cells and NK cells after the rituximab infusion. (A) Peripheral blood smear after the rituximab infusion showed pancytopenia with marked leukopenia secondary to moderate neutropenia (850/μl) and marked lymphocytopenia (150/μl). Bar represents 20 μm. Flow cytometry showed the presence of CD3+/CD5+ T cells (B) with CD4:CD8 ratio of 6.1 (C) and NK cells (D) but the absence of CD19+/CD20+ B cells (E) and CD38^{high} plasma cells (F)

protocol was initiated in the emergency room, and the patient was started on vancomycin, aztreonam (due to penicillin allergy), and levofloxacin (due to local hospital's antibiogram for *Pseudomonas*). Extensive infectious workups were performed including blood and urine cultures, COVID-19 tests twice on March 8 and March 10, 2021, tests for Hepatitis B, influenza A, influenza B, respiratory syncytial virus, Biofire FilmArray Respiratory Panel, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Streptococcus pneumoniae*. All tests returned as negative. CT chest, abdomen, and pelvis also did not reveal any possible source of infection. Therefore, antibiotics were discontinued, and patient was discharged 3 days later. Flow cytometry of peripheral blood during the hospitalization (Table 1) confirmed that among the lymphocytes (23.1% of total cell counts), 98.7% were CD3+/CD5+ T cells (Figure 2B) with CD4:CD8 ratio of 6.1 (Figure 2C), 0.9% were natural killer (NK) cells (Figure 2D) while there was no CD19+/CD20+ B cells (0%, Figure 2E) or $CD38^{high}$ plasma cells (0%, Figure 2F). Despite the history of WM, there was no evidence of clonality since the B cells were virtually absent. Patient's blood cell counts gradually recovered (Table 1). However, flow cytometry performed on March 29, 2021 (Day 22 since rituximab infusion), and April 28, 2021 (Day 53 since rituximab infusion), continued showing that B cells were virtually absent and there was no diagnostic immunophenotypic abnormalities detected (Table 1). Patient is currently under surveillance with monthly peripheral blood flow cytometry. Treatment for his WM will be reconsidered when there is evidence of WM relapse.

3 | DISCUSSION

We described a case in which a patient developed acute lympholysis and pancytopenia within hours upon receiving rituximab infusion. Approximately 4 years prior, the patient tolerated rituximab therapy well for 2 years. This response upon rituximab re-initiation was very likely related to receiving the second dose of Moderna COVID-19 vaccine 10 days before. Patient did not present with signs or symptoms of typical acute infusion reactions or anaphylaxis characterized by fever, hypotension, bronchospasm, urticaria, and angioedema. Immune hemolytic anemia and severe disseminated intravascular coagulation (DIC) were ruled out by within-normal-range haptoglobin and fibrinogen, respectively. Tumor lysis syndrome was unlikely since patient did not develop hyperkalemia, hyperphosphatemia, hyperuricemia, or hypocalcemia. Patient demonstrated baseline mild anemia and thrombocytopenia before the treatment, but the acute worsening of pancytopenia cannot be explained by bone marrow suppression due to his WM. Patient also did not present with any sign or symptoms such as headache, vertigo, vision change, and spontaneous mucosal bleeding suggesting a hyperviscosity state from his WM. Infection and sepsis were also ruled out by extensive infectious workups. Given that the patient recently received his second dose of Moderna COVID-19 vaccine 10 days before the rituximab infusion, and the secondary immune response after the booster immunization usually peaks between 7 and 30 days,[10] the most plausible explanation for his clinical presentation is the hyperacute depletion of large number CD20+ B cells and plasma cells by rituximab suggested by decreased serum complement component 3 level and complement component 4 level (Table 1). This massive hyperacute depletion of B cells and plasma cells likely caused the subsequent cascade events including cytokine release syndrome or cytokine storm[11] suggested by elevated serum interleukin-6 level and serum interleukin-2 receptor alpha chain level (Table 1), cytokine-induced tissue damage, coagulopathy (INR 1.3, normal PTT, d-dimer 3.35 mcg/ml with reference range ≤0.49 mcg/ml), acute-phase physiological changes, or immune cell-mediated collateral damage. All these events can presumably lead to pancytopenia.

Patient reported similar symptomatic presentations and a 4-day hospital admission after he received the influenza vaccine on October 20, 2016. However, his last infusion of rituximab before the influenza vaccine was on June 29, 2016 (Figure 1), almost 4 months before the vaccination. The laboratory results from that admission revealed severe neutropenia (absolute neutrophil count remained zero for 3 days before starting to recover), distinguishing from lymphocytopenia seen in the current event. It was most likely that after repetitive rituximab infusions, the influenza vaccine elicited late-onset neutropenia and acute neutropenic fever without severely worsening lymphocytopenia, anemia, or thrombocytopenia. A very similar case was reported previously.[12] Rituximab-induced late-onset neutropenia usually occurs at least three to 4 weeks following the end of rituximab administration.[5] It has also been reported that rituximab may induce neutropenia up to 474 days after the end of treatment.[13]

It has been recognized that rituximab can impact the efficacy of various vaccines, and some organizations have proposed general recommendations on the timing of rituximab treatment relative to the COVID-19 vaccination. However, the potential acute consequences when patients receive both rituximab and the COVID-19 vaccine have not been sufficiently appreciated and the current guidelines on COVID-19 vaccination for patients receiving anti-CD20 therapies need to be updated urgently. Therefore, we propose:

1. If systemic anti-CD20 therapy is necessary for newly diagnosed or relapsed malignancies or maintenance therapy and the benefits of COVID-19 prevention does not outweigh the benefits of anti-CD20 therapy, COVID-19 vaccination should be postponed until 3 months (4 half-lives of rituximab in vivo) after the completion of anti-CD20 therapy or the B-cell counts have recovered to over 0.5×10^3 cells/μl.

2. If the patient has already received the COVID-19 vaccine, systemic anti-CD20 antibody therapy should be given 4 weeks or more after the last vaccination to avoid the massive depletion of large numbers of CD20+ B cells and plasmas cells produced within 30 days after the vaccination.[10] If urgent treatment for malignancy is needed, alternative therapy such as cytotoxic chemotherapy should be considered.

It might be reasonable to extrapolate these recommendations to anti-CD19, anti-CD38, anti-CD138, and anti-CD319 (anti-SLAMF7) therapies and to vaccines other than COVID-19 vaccines, especially vaccinations requiring booster doses. Certainly, more clinical data or studies are needed to refine the recommendations and guidelines more precisely for different vaccines and different therapies.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

VSL and YL: wrote the manuscript; YL: performed data collection and data analysis.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable—no new data are generated.

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