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Letter

Vasculitis as Temporally Associated With COVID-19 Infection or Vaccination: A Single-center Experience

To the Editor:

Vasculitis has been recognized as an organ-specific immune-mediated complication of the SARS-CoV-2 infection, and the number of reported coronavirus disease 2019 (COVD-19)–associated vasculitis cases is gradually increasing.[1] Vasculitis can develop early after the onset of COVID-19 (an interval of < 2 weeks) or manifest later during the course of the disease, and it is associated with a significant morbidity. The recent review of 19 vasculitic cases following COVID-19 reported the need for intensive care treatment in 31% and death in 16% of cases.[1]

Lacking specific antiviral treatment, the best strategy to stop the pandemic currently relies on timely and adequate immunization worldwide. COVID-19 vaccines proved to be efficacious and safe in the registration studies, their benefits largely outweighing the risk of rare potential complications.[2] Nevertheless, immunization may induce de novo autoimmune diseases, particularly in genetically predisposed individuals. Indeed, reports of vasculitis (most commonly cutaneous vasculitis and IgA vasculitis) following vaccination (most frequently influenza vaccine) have been documented.[3,4] Just recently, a flare of skin leukocytoclastic vasculitis and a case of antineutrophil cytoplasmic antibody (ANCA) glomerulonephritis following COVID-19 vaccination have been described.[5,6]

Here we describe a cohort of 15 patients with vasculitis temporally associated with COVID-19 disease and/or COVID-19 vaccine. This study was approved by the Slovenian National Medical Ethics Committee (approval number

Table 1. Characteristics of patients with vasculitis following COVID-19 infection or immunization.

No.	Age Range, yrs	Prior Rheumatic Disease	COVID-19	Vaccine	Interval[a]	Presentation	Investigation	Vessel Size	Diagnosis	Therapy	Outcome
1	60s	No	Yes[b]	No	2 weeks	Skin purpura, arthritis	Histology	Small	IgAV	GC	Recovery
2	80s	No	Yes[c]	No	6 weeks	Constitutional symptoms	Lung HRCT, anti-MPO+	Probably small	AAV	GC, CYC	Deceased
3	50s	SLE	Yes[c]	No	3 weeks	Systemic inflammatory response	CTA, PET/CT	Large[d]	LVV	GC, CYC	Recovery
4	60s	No	Yes[c]	No	3 weeks	Systemic inflammatory response	CTA, PET/CT	Large[e]	LVV	GC	Recovery
5	80s	No	Yes[c]	No	Concurrent	Limb gangrene, skin necroses	Histology	Medium and small	Necrotizing vasculitis	GC	Deceased
6	60s	No	Yes[c]	No	8 weeks	Paniculitis and skin necroses	Histology	Small	Necrotizing vasculitis	GC	Recovery
7	40s	No	Yes[c]	No	2 weeks	Skin purpura	Histology	Small	Skin vasculitis	Local GC	Recovery
8	80s	No	No	Pfizer-BioNTech	7 days	Myalgia	Histology	Small	Myositis, arteritis	GC	Recovery
9	40s	No	No	AstraZeneca	8 days	Skin purpura, arthritis	Histology	Small	IC vasculitis	NSAID	Recovery
10	70s	No	No	Pfizer-BioNTech	10 days	Constitutional symptoms	US	Large	GCA	GC	Recovery
11	60s	No	No	AstraZeneca	9 days	Skin purpura	Histology	Small	IC vasculitis	GC	Recovery
12	60s	No	No	Pfizer-BioNTech	16 days	Painful left TA	US	Large	Left TA vasculitis	GC	Recovery
13	20s	No	No	Moderna	8 days	Skin purpura	Histology	Small	IC vasculitis	Local GC	Recovery
14	70s	No	No	Pfizer-BioNTech	20 days	Headache, yaw claudication	US	Large	GCA	GC	Recovery
15	50s	No	Yes[c]	Pfizer-BioNTech	2 weeks[f]	Carotidinia (left side)	US, CTA	Large[g]	Carotid artery arteritis	GC	Recovery

[a] From infection/vaccination to vasculitis. [b] Serological test. [c] PCR test. [d] Aorta, carotid, subclavian, axillary, brachial, mesenteric, iliac arteries. [e] Aorta, axillary, brachial iliac arteries. [f] From infection to vasculitis. [g] Segmental left carotid artery. anti-MPO: antimyeloperoxidase; AAV: antineutrophil cytoplasmic autoantibody–associated vasculitis; COVID-19: coronavirus disease 2019; CTA: computed tomography arteriography; CYC: cyclophosphamide; GC: glucocorticoid; GCA: giant cell arteritis; HRCT: high resolution computer tomography; IC: immune complex; IgAV: IgA vasculitis; LVV: large vessel vasculitis; NSAID: nonsteroidal antirheumatic drug; PET/CT: positron emission tomography/computed tomography; SLE: systemic lupus erythematosus; TA: temporal artery; US: ultrasound.

0120-554/2020/3). Patient written informed consent was obtained.

Our department provides rheumatological care at the secondary level in a region of approximately 720,000 adult residents. In addition, we are 1 of the 2 tertiary centers in the country, servicing approximately 1.5 million people of the Slovenian population. Patients with systemic vasculitides have been systematically followed at our department for more than a decade. In the present study, we aimed to analyze cases of de novo vasculitis temporally associated with COVID-19 infection and after COVID-19 vaccination. Between March 13, 2020, and June 15, 2021, there have been 94,352 COVID-19 cases documented among adult residents in a region serviced at secondary level. By June 15, 2021, there were 341,406 residents in the region who received at least 1 dose of 4 the different COVID-19 vaccines currently available in the country: 2 mRNA vaccines (Pfizer-BioNTech and Moderna), and 2 vector vaccines (Oxford/AstraZeneca and Janssen/Johnson & Johnson). During the study period, we diagnosed 7 patients with COVID-19–associated vasculitis (infection was proven using a PCR test in 6 patients and serologically in 1 patient; Table 1, patients 1–7), and we documented 7 cases of vasculitis temporally related to COVID-19 immunization (Table 1, patients 8–14). In addition, 1 patient (Table 1, patient 15), who was diagnosed with COVID-19 a day after receiving the second dose of COVID-19 vaccine, also developed vasculitis 2 weeks after their proven infection.

While 1 patient with COVID-19–associated vasculitis had a prior rheumatic disease (systemic lupus erythematosus), none of the other patients had any history of rheumatic disease. Vasculitis commonly manifested 2–8 weeks after the first symptoms of COVID-19 and was concurrent with the diagnosed infection in only 1 patient. Vasculitis associated with COVID-19 vaccination followed, with a delay of 7–20 days after immunization. Regarding the clinical presentation and the size of affected vessels, skin-limited small vessel vasculitis and large artery involvement prevailed in both groups. All patients with vasculitis following COVID-19 infection, except 1 with skin-limited disease, were treated with systemic glucocorticoids. Two patients with COVID-19–associated vasculitis received cyclophosphamide additionally. During the active vasculitis, 2 patients with COVID-19–associated vasculitis died (due to active vasculitis in 1 and treatment-related complications [pneumocystis pneumonia]) in the other). Vasculitis remitted with local and/or systemic treatment in all patients with the COVID-19 vaccine–associated disease.

Vasculitides are rare, heterogeneous, and mostly idiopathic autoimmune diseases. Those associated with a probable etiology (e.g., connective tissue disease; malignancy; various environmental triggers including infections, toxins, or the use of specific medications) represent a distinct subgroup of vasculitides in the current Chapel Hill consensus conference nomenclature.[7] In conjunction with the novel SARS-CoV-2 virus, over 70 different, more or less severe, systemic and/or organ-specific immune-mediated complications have been reported, vasculitis being one of them.[1]

Although we could not confirm the causality nor the coincidence between a COVID-19 infection or vaccine and vasculitis, we believe that both should be considered as risk factors for inducing and/or promoting systemic vasculitis.

The pathogenic mechanisms of COVID-19–associated vasculitis have not been elucidated as yet. One could hypothesize molecular mimicry, hyperactivation/bystander activation of the immune system, loss of immune tolerance, neoantigen formation, and antibody triggering.[8] All these mechanisms might also play a role in COVID-19 vaccine–associated vasculitis. The multifaceted and subtle interplay between infections, vaccinations, and autoimmunity should be further explored.

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The authors declare no conflicts of interest relevant to this article.

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DATA SHARING POLICY

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

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