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Eosinophil-associated disease after SARS-CoV-2 infection or vaccination: EGPA and related entities

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To the editor,

We are writing to express our concerns regarding a potential link between SARS-CoV-2 infection or vaccination and the development of de novo eosinophil-mediated inflammation, including eosinophilic granulomatosis with polyangiitis (EGPA). Recently, we have observed a few such cases at our institution. Several mechanisms have been proposed to explain autoimmunity in the context of viral illness or vaccination. Infection with the SARS-CoV-2 virus leads to endothelial dysfunction (1). This endothelial dysfunction may be characterized by extensive neutrophil infiltration and formation of neutrophil extracellular traps at the sites of infection, which may lead to a proinflammatory environment. This may, in turn, lead to development of autoantibodies, such as antineutrophil cytoplasmic antibodies (ANCAs), or other immune responses (2). Molecular mimicry in which viral antigens resemble self-proteins is a potential mechanism for the induction of autoantibodies. We describe 7 cases of eosinophil-mediated inflammation—some fulfilling the diagnostic criteria for EGPA—identified shortly after SARS-CoV-2 infection or vaccination. We screened the electronic health records of adult patients (≥18 years) seen at our institution between January 1, 2020, and August 1, 2022, for documentation of "eosinophilia." The review was conducted to identify patients with new or relapsed EGPA (as defined by the 2022 American College of Rheumatology criteria) or other eosinophil-predominant inflammatory processes who had symptom onset within 90 days after SARS-CoV-2 exposure (infection or vaccination). Patients with preexisting lung disease (eg, lung cancer or metastases, interstitial lung disease, bronchiectasis, or chronic obstructive pulmonary disease) or those with treatment nonadherence were excluded from analysis. Of 2,528 patients initially identified, 106 met the diagnostic criteria for eosinophil-mediated inflammation, of whom 7 (5 men and 2 women) had symptom onset within 90 days after SARS-CoV-2 vaccination (n=6) or infection (n=1) (Table 1). Four of the patients met the full criteria for EGPA diagnosis. The other 3 patients had eosinophil-predominant inflammation without definitive ANCA positivity or histologic vasculitis. The differential diagnoses for the 3 non-EGPA cases included a broader spectrum of eosinophil-associated conditions, such as vaccine-related hypersensitivity reaction, eosinophilic pneumonia, and hypereosinophilic syndrome. The median (range) patient age was 54 (22-76) years, and the median (range) body mass index was 24 (23-34). None of the patients had a prior diagnosis of EGPA or a related disorder. Three patients had a history of asthma, 2 had chronic sinusitis, and 1 had allergic rhinitis. Two patients were former smokers, and 1 used smokeless tobacco.

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Table 1. Demographic and Clinical Characteristics, Laboratory Test and Pathologic Findings, and Treatments

Patient No.	Age, y	Sex	Smoking history	Vaccination/ infection	System involved	ANCA	Peripheral eosinophils, $\times 10^9$/L[a]	Exhaled NO, ppb[b]	IgE, kU/ L[c]	BAL	Biopsy findings indicative of EGPA	Treatment
ANCA positivity												
1	53	M	Former (smokeless tobacco)	BNT162b2 (second dose)	Pulmonary Sinus disease Neurologic	Positive (p-ANCA, MPO)	0.20	9	31	NA	Hilar lymph node (nonnecrotizing granuloma)	Corticosteroid Rituximab
2	22	M	Never	BNT162b2 (second dose)	Pulmonary Sinus disease	Positive (p-ANCA) Negative (MPO)	1.87	165	NA	Normal	NA	Corticosteroid Mepolizumab
3	54	M	Former smoker (20 pack y)	Ad26.COV2.S (first dose)	Pulmonary Neurologic Sinus disease Muscle	Positive (p-ANCA, MPO)	10.38	NA	1,362	NA	Peripheral nerve and interstitium (microvasculitis)	Corticosteroid Mepolizumab Rituximab
4	76	F	Never	2019-nCoV mRNA-1273 (second dose)	Pulmonary	Positive (p-ANCA, MPO)	4.26	26	NA	29% eosinophilia	TBB (organizing pneumonia with high eosinophils)	Corticosteroid Benralizumab Mepolizumab
ANCA negativity												
5	60	F	Never	Infection	Pulmonary Sinus disease	Negative	0.56	99	NA	NA	Sinus (chronic inflammation, severe eosinophils)	Corticosteroid
6	64	M	Former smoker	2019-nCoV mRNA-1273 (third dose)	Pulmonary Cardiac	Negative	14.21	NA	1,995	76% eosinophilia	TBB (eosinophilic inflammation) Endomyocardial (eosinophilic myocarditis)	Corticosteroid Mepolizumab
7	53	M	Never	Ad26.COV2.S (first dose)	Pulmonary Sinus disease	Negative	3.01	64	15	NA	NA	Corticosteroid Mepolizumab

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BAL, bronchoalveolar lavage; EGPA, eosinophilic granulomatosis with polyangiitis; F, female; IgE, immunoglobulin E; M, male; MPO, antimyeloperoxidase antibody; NA, not available; NO, nitric oxide; p-ANCA, perinuclear ANCA; ppb, parts per billion; TBB, transbronchial biopsy.

[a]Reference range: 0.03-0.48$\times 10^9$/L.

[b]Reference: <39 ppb.

[c]Reference: <214 kU/L.

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Eosinophil-mediated inflammatory symptoms developed within 1 month after SARS-CoV-2 exposure for all patients. Respiratory symptoms were present in all patients by the time they were seen at our institution. These symptoms included dyspnea, cough, sputum production, and wheezing. Constitutional symptoms, such as fatigue, night sweats, and weight loss, were reported by 5 patients. New or worsening sinus symptoms were reported by 4 patients, and neurologic symptoms, including numbness and generalized weakness, were reported by 2 patients. Chest computed tomography was performed for all patients, and the findings included bronchial wall thickening, mucous plugs, pulmonary nodules, infiltrates (ie, consolidation and ground-glass opacities), and mediastinal lymphadenopathy. Sinus computed tomography was obtained for all patients except 2 (Nos. 4 and 6), which all had findings consistent with sinusitis. One patient had cardiac involvement, which included chest pain and an elevated troponin level. Eosinophilic myocarditis was diagnosed for this patient on the basis of peripheral eosinophilia and myocardial biopsy findings. Three patients reported skin rashes, but only 1 had a skin biopsy finding of atopic dermatitis. Kidney involvement was not observed for any patients. Four patients had perinuclear ANCA (with, antimyeloperoxidase antibody) positivity (Table 1). Five patients had peripheral eosinophilia ($>1\times10^9$/L), and 2 had increased immunoglobulin E levels (≥214 kU/L) during the eosinophil-mediated disease course. Oral exhaled nitric oxide was increased (≥39 parts per billion) in 3 patients. Three patients underwent bronchoscopy with bronchoalveolar lavage, of whom 1 (No. 2) had normal findings and 2 (Nos. 4 and 6) had eosinophilia (29% and 76%, respectively). Three patients had lung biopsy performed. Transbronchial biopsy findings showed eosinophilic inflammation for 2 patients (Nos. 4 and 6) (Table 1). Mediastinoscopy-mediated hilar lymph node biopsy for 1 patient (No. 1) showed nonnecrotizing granuloma. Extrapulmonary biopsies were performed for 3 patients. This included nasal biopsies for 2 patients, with chronic inflammation with severe eosinophilia evident for 1 patient (No. 5) and nondiagnostic findings for the other 2 patients. Results from pulmonary function tests were available for 6 patients, of whom 4 had evidence of obstruction. Electromyography was performed for 3 patients, with findings suggestive of mononeuritis multiplex in 2 patients. One patient (No. 3) underwent nerve biopsy, which showed a severe, generalized reduction in myelinated fiber density with increased late axonal degeneration. Perivascular mononuclear infiltrates with vessel wall infiltration, separation, and fragmentation indicated active microvasculitis with ongoing inflammatory changes and neovascularization. To rule out other causes of eosinophilia, 2 (Nos. 6 and 7) of the 3 patients with ANCA-negative disease underwent targeted examinations. Both patients underwent bone marrow biopsy, which showed no evidence of clonal myeloid or lymphoproliferative disease. They also underwent cytogenetic testing for chronic eosinophilia-associated genetic variations in the *CHIC2*, *PDGFRB*, *FGFR1*, *JAK2*, and *ABL1* genes, all of which were negative for disease-causing variations. These patients also underwent stool examination for ova and parasites, with negative results. One patient had a normal serum tryptase level, reducing concern for a mast cell disorder. All patients in our cohort received corticosteroid therapy, with variable doses and durations (Table 1). Five patients were treated with interleukin 5 inhibitors, such as mepolizumab. Rituximab was administered to 2 patients (Nos. 1 and 3). One patient (No. 3) required treatment with a combination of corticosteroids, mepolizumab, and rituximab. All patients had favorable outcomes, with improved respiratory status after treatment initiation and no deaths. One patient (No. 4) had residual neuropathy. Chan-Chung et al (3), Costanzo et al (4), and Ibrahim et al (5) published case reports or series of either relapsed or de novo EGPA identified after SARS-CoV-2 infection or vaccination. Presenting neurologic symptoms were frequent and pronounced in these reports. For our patients, pulmonary symptoms were more common, and only 2 patients had neurologic involvement. Notably, a history of asthma in 3 of our patients may have predisposed them to EGPA. One study reported that the rate of antimyeloperoxidase and antiproteinase 3 antibody positivity in patients with SARS-CoV-2 infection was 12.4% and 7.9%, respectively (6). However, no clinically meaningful effects on 3 investigated outcomes (severe infection, mechanical ventilator care, and death) were apparent. In contrast, another study reported that ANCA positivity in hospitalized patients with COVID-19 was associated with poor clinical outcomes and increased complications (1). The findings reported here are limited by their retrospective nature and a limited follow-up period because most

of the patients were seen for consultations at our tertiary care institution. One patient received a SARS-CoV-2 booster vaccination after recovery of EGPA without recurrence of vasculitic symptoms. Although we cannot infer causality between SARS-CoV-2 exposure and eosinophil-mediated inflammation, the temporal association and clinical consistency suggest that SARS-CoV-2 may act as a trigger for eosinophilic inflammation, including EGPA.

In conclusion, eosinophilic inflammation may occur after SARS-CoV-2 exposure. EGPA should be considered when systemic symptoms, eosinophilia, and ANCA positivity are present, but other eosinophil-associated conditions may also be present in this clinical context and warrant further consideration.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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References

1. Kadkhoda K, Laurita K. Antineutrophil cytoplasmic antibodies and their association with clinical outcomes in hospitalized COVID-19 patients. Cell Death Discov. 2021;7(1):277. doi: 10.1038/s41420-021-00671-1
2. Nakazawa D, Shida H, Tomaru U, et al. Enhanced formation and disordered regulation of NETs in myeloperoxidase-ANCA-associated microscopic polyangiitis. J Am Soc Nephrol. 2014;25(5):990-7. doi: 10.1681/ASN.2013060606
3. Chan-Chung C, Ong CS, Chan LL, Tan EK. Eosinophilic granulomatosis with polyangiitis after COVID-19 vaccination. QJM. 2022; 114(11):807-9. doi: 10.1093/qjmed/hcab273
4. Costanzo G, Ledda AG, Ghisu A, Vacca M, Firinu D, Del Giacco S. Eosinophilic granulomatosis with polyangiitis relapse after COVID-19 vaccination: a case report. Vaccines (Basel). 2021;10(1):13. doi: 10.3390/vaccines10010013
5. Ibrahim H, Alkhatib A, Meysami A. Eosinophilic granulomatosis with polyangiitis diagnosed in an elderly female after the second dose of mRNA vaccine against COVID-19. Cureus. 2022;14(1):e21176. doi: 10.7759/cureus.21176
6. Lee LE, Jeong W, Park YB, Jeong SJ, Lee SW. Clinical significance of antineutrophil cytoplasmic antibody positivity in patients infected with SARS-CoV-2. J Clin Med. 2022;11(14):4152. doi: 10.3390/jcm11144152