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The Association of Polymyalgia Rheumatica and Giant Cell Arteritis With COVID-19 Vaccination: A Systematic Review

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Abstract

Background: Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are interrelated inflammatory conditions, and evidence suggests that infection and vaccination might act as a trigger for these conditions. This descriptive systematic review summarizes the published case reports and case series on new-onset PMR and GCA following COVID-19 vaccination, highlighting their clinical features, diagnostic findings, and treatment outcomes.

Objectives: To do a systematic analysis of available literature regarding the association between COVID-19 vaccination and the first onset or flare of PMR and/or GCA.

Design: Systematic review of case reports and case series.

Data sources and methods: A systematic literature search was conducted using PubMed/MEDLINE, Cochrane, ScienceDirect, and Google Scholar. Data on patient demographics, clinical features, outcomes, and latency periods were extracted and analyzed. Quality assessment of included studies was performed using the Joanna Briggs Institute Critical Appraisal Tool.

Results: A total of 32 articles, documenting 50 new-onset cases (30 PMR and 20 GCA), were identified for inclusion. The mean age for patients with PMR was 71.06 years, and 72.85 years for GCA. A slight female predominance was observed (60%) for both PMR and GCA. Pfizer-BioNTech (48%) and AstraZeneca (38%) vaccines were most frequently associated with disease onset. The mean latency period from vaccination to symptom onset was 11.03 days for PMR and 5.3 days for GCA, indicating a temporal relationship. Most of these studies originated from North America and Europe mimicking the global scale of vaccination. Most patients responded well to symptomatic treatment with corticosteroids.

Conclusions: There exists a temporal association between COVID-19 mRNA or viral vector-based vaccines and the onset of PMR and GCA. While causality is not proven, this review underscores the need for clinicians to be aware of this potential association to ensure timely diagnosis and treatment, particularly as booster vaccinations continue to be administered. Larger epidemiological studies with long-term follow-up are essential to further explore this association.

Keywords

COVID-19 vaccination, polymyalgia rheumatica, giant cell arteritis, temporal arteritis, vasculitis

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Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are interrelated inflammatory conditions, often referred to as GCA-PMR spectrum disease (GPSD).[1] Polymyalgia rheumatica is characterized by significant pain and stiffness, commonly affecting the neck, shoulder, hips, upper arms, and thighs, whereas GCA is a large-vessel vasculitis that primarily affects, but is not limited to, the

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temporal artery and can lead to severe complications including vision loss.[2,3] While the exact etiology of these diseases is largely unknown, there exists an association between them as 16% and 21% of patients with PMR go on to develop GCA, whereas PMR is present in 40% and 60% of individuals with a diagnosis of GCA. Polymyalgia rheumatica is commonly observed as a clinical manifestation in individuals with GCA; however, it can also present as an isolated condition. Although less frequent, some patients with isolated PMR may subsequently develop GCA.[4] Evidence suggests that infections and vaccinations might act as triggers for these conditions.[5,6]

Since the emergence of the SARS-CoV-2, a record of greater than 775 million cases and more than 7 million deaths have been reported worldwide.[7] Soon after the emergence of COVID-19 disease, several vaccines were developed and a worldwide vaccination drive was initiated. According to World Health Organization, more than 13 billion doses of COVID-19 vaccination have been administered globally with an estimated 14.4 million lives being saved as a result.[8] However, as part of the pandemic, 2 processes, namely infection and vaccination, have compounded the incidence of immune-mediated diseases which are known to be triggered by these processes. More specifically, the likely association between the COVID-19 vaccines and the incidence of PMR and GCA is an area of growing interest. Initial studies have reported the occurrence of PMR and GCA shortly after the administration of vaccination-indicative of at least a temporal association between the two.[9] Given the widespread administration of vaccines, it is crucial to understand whether there exists a causative link or whether these instances were incidental.

The rapidly emerging literature on this topic warrants a systematic analysis of all available literature regarding the association between COVID-19 vaccination and the first onset or flare of PMR and/or GCA. By examining the clinical presentations, potential pathophysiological mechanisms and triggers, and outcomes, this review seeks to provide a comprehensive overview of currently available evidence. Understanding this potential association is essential for guiding clinical practice and familiarizing clinicians with this important association. Awareness of this association will allow timely diagnosis and improve outcomes by preventing late-stage complications such as vision loss. This is particularly important in the context of booster doses for COVID-19 being administered on a large scale and regional surges in COVID-19 cases continuing. This review also aims to identify gaps in the current knowledge and suggest directions for future research to further elucidate the potential risks associated with COVID-19 vaccination in predisposed individuals. To the best of our knowledge, this is the first systematic review to provide an in-depth analysis of GPSD secondary to COVID-19 vaccination.

Methods

This systematic review is fully compliant with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines.[10] As this is a retrospective analysis of published data, institutional ethics approval was not required. The authors confirmed that patient consent for publication of their cases was obtained in the included studies.

Search strategy

A systematic literature search was conducted using 4 databases: PubMed/MEDLINE, Cochrane, ScienceDirect, and Google Scholar from inception till July 3, 2024. The search was designed to capture all relevant literature using a combination of keywords and MeSH terms, including but not limited to "COVID-19," "SARS-CoV-2," "Polymyalgia Rheumatica," "PMR," "Giant Cell Arteritis," "GCA," "temporal arteritis," "large vessel vasculitis," and "COVID-19 vaccine." Boolean operators (AND/OR) were applied as relevant. No hand-searching of reference lists or snowballing techniques were performed as part of the search. The complete search strategy for each database is detailed in Supplementary files.

Eligibility criteria

Articles were included if they (1) were published case reports or case series reporting cases of PMR or GCA following COVID-19 vaccination; (2) reported patient cases that fulfilled the ACR/EULAR criteria for PMR (2012) or GCA (2022) following COVID-19 vaccination[11,12]; and (3) provided sufficient clinical, diagnostic, and treatment outcome details. Articles were excluded if they (1) did not report individual case data or were not original studies (eg, reviews, editorials, or letters without case details), (2) included cases that did not meet the ACR/EULAR classification criteria for PMR or GCA, (3) were duplicate publications or studies with overlapping data that did not provide additional unique information, or (4) lacked key clinical or diagnostic details, making the data unclear or insufficient. No restrictions in terms of time frame, original study design, language, or country of publication were applied, allowing for a comprehensive retrieval of relevant studies.

For the purposes of this review, "post-vaccination" was defined as any new onset of PMR or GCA symptoms following vaccination, as reported by study authors, without imposing a predefined maximum latency period. Onset intervals were recorded as stated in each source. This inclusive approach was chosen to capture the full range of reported onset intervals, recognizing variability in individual immune responses and case definitions.

In terms of outcomes, complete remission was defined as the complete resolution of clinical symptoms along with normalization of inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) that permitted tapering of corticosteroid therapy to a low maintenance dose without subsequent disease flares for at least 3 months. Partial remission was defined as significant improvement in clinical symptoms and reduction in inflammatory markers; however, residual symptoms or the need for moderate-dose maintenance therapy persisted.

Study selection and data extraction

The study selection process was carried out according to the PRISMA statement. Initial records identified from the search were imported into Mendeley and deduplicated. Three independent reviewers (MZA, FA, and ZA) screened the remaining records, selecting studies based on predefined inclusion criteria. References of included articles were also curated to identify additional relevant studies, if any. Data were extracted and organized into 3 tables: Table 1 details demographic data, clinical features, and outcomes for cases with PMR; Table 2 details demographic data, clinical features, and outcomes for cases with GCA; and Table 3 compares common features of both. Continuous variables were expressed as means ± standard deviations, whereas categorical variables were reported as absolute numbers and percentages. Microsoft Excel was used for data management and analysis. References were managed using Zotero.

Quality assessment

The quality of the included studies was assessed using the Joanna Briggs Institute Critical Appraisal Tool.[45] Two reviewers (HS and MZA) independently evaluated each study and reached a consensus on the quality scores. The detailed quality assessment report is included in the Supplementary files. Due to the nature of the included studies (case reports and case series), a meta-analysis was not conducted.

Results

Study characteristics

This systematic review included 32 articles, comprising 22 case reports and 10 case series, documenting 30 cases of PMR and 20 cases of GCA temporally associated with COVID-19 vaccination.[13-44] The PRISMA flow diagram (Figure 1) demonstrates sequential steps in the inclusion of articles. Most of these studies originated from North America and Europe, reflecting the global scale of the magnitude of vaccination. The studies varied in patient numbers, symptom severity, and outcomes, offering a broad overview of these conditions postvaccination.

Patient demographics

The review identified 30 patients with PMR and 20 patients with GCA. For both groups, the cohort had a slight female predominance, with approximately 60% females and 40% males, and a mean age of 71.06 ± 6.14 years for patients with PMR and 72.85 ± 6.82 years for patients with GCA.

Among the vaccines reported, Pfizer-BioNTech and AstraZeneca were most commonly associated with the onset of PMR and GCA, representing approximately 48% and 38% of cases, respectively. The mean latency period from vaccination to symptom onset was 11.03 ± 8.89 days for PMR and 5.3 ± 5.62 days for GCA.

Clinical and diagnostic findings

Giant cell arteritis is commonly presented with a range of symptoms. Most frequently reported symptoms were new-onset headache (70%), jaw claudication (35%), constitutional symptoms such as fever, weight loss, and fatigue (80%), scalp tenderness (35%), and visual symptoms including transient or permanent vision loss (20%). On the contrary, PMR primarily presents with bilateral aching and morning stiffness in the shoulders, hip girdles, neck, and torso. Shoulder pain was present in 93.3% of patients, hip pain in 80%, and decreased range of motion in 40%. The latency period between vaccination and onset of symptoms was reported in 28/30 PMR cases. The shortest interval was 1 day, whereas the longest was 45 days (in one case only) with a mean latency period of 11.03 ± 8.89 days. Similarly, 20/20 GCA cases reported the time interval from vaccination to onset of symptoms which ranged from 6 hours to 21 days with a mean latency period of 5.3 ± 5.62 days. Diagnostic findings were standard for both diseases with no peculiarity. For GCA, elevated ESR and CRP were notable findings, with mean values reported at 83.09 ± 35.81 mm/h and 89.20 ± 70.40 mg/L, respectively. Imaging, including positron emission tomography/computed tomography scans and temporal artery ultrasounds, frequently demonstrated large-vessel inflammation (observed in 13 out of 20 cases) characteristic of GCA. Polymyalgia rheumatica also showed significant elevation in these inflammatory markers, with mean ESR levels at 87.63 ± 27.99 mm/h and mean CRP levels at 109.21 ± 132.39 mg/L. Imaging studies often revealed bursitis and tenosynovitis, particularly in the shoulder and hip regions.

Treatment and clinical outcomes

Corticosteroid therapy was administered in 29 (96.66%) cases of PMR leading to significant symptom relief and normalization of inflammatory markers. One patient (3.33%) received acetaminophen alone with complete recovery. A small proportion of patients (n = 3, 10%) also received methotrexate (MTX). Corticosteroids were the primary treatment in all the cases of GCA, with additional immunosuppressive therapies like MTX or tocilizumab (administered in 2 and 4 cases, respectively) administered in a small subset of patients. Glucocorticoid dosing varied considerably across the studies, reflecting individualized treatment strategies. In PMR cases, initial prednisone/prednisolone doses ranged from 15 to 60 mg daily, with most patients starting at 15 to 40 mg/day and undergoing gradual tapering over weeks to months, whereas in GCA cases, initial glucocorticoid regimens varied widely, with oral prednisone/prednisolone doses ranging from 30 to 65 mg daily, often with gradual tapering over months. Intravenous methylprednisolone is typically administered at 500 to 1000 mg/day for 3 to 5 days before transitioning to oral therapy. The detailed breakdown of individual patient regimens is provided in Supplemental Table 1 (PMR) and Supplemental Table 2 (GCA).

Table 1. Demographic characteristics and clinical features of cases reported as PMR following COVID vaccinations.

		Vaccination		Clinical features									
Authors	Age, sex	Vaccine, doses	Latency, d	Morning stiffness	Shoulder stiffness	Hip pain	Range of movement	Other joints involvement	GCA symptoms	Inflammatory markers	Imaging	Treatment	Outcomes
Ahmad and Baker[13]	72, F	Pfizer-BioNTech, 3	10	N	Y	Y	n/r	N	Temporal Headache	ESR: 108 mm/h; CRP: 150 mg/L	n/r	Steroids	Improvement
Al-Allaf et al[14]	63, F	mRNA COVID-19 vaccine, 1	n/r	Y	Y	N	n/r	N	Left sided temporal headache, jaw claudication	ESR: 150 mm/h	n/r	Steroids	Relapse
Cadiou et al[15]	71, M	Pfizer-BioNTech, 2	14	Y	Y	Y	n/r	N	N	CRP: 55 mg/l	**USG:** subdeltoid bursitis and biceps tenosynovitis	Steroids	improvement
Furr and Garg[16]	69, F	Moderna, 2	-	N	Y	Y	n/r	N	N	ESR: 68 mm/h; CRP: 31.1 mg/L	n/r	Steroids	Improvement
Furr and Garg[16]	74, M	Pfizer-BioNTech, 3	20	N	Y	Y	↓	Neck	N	ESR: 24 mm/h; CRP: 73.2 mg/L	n/r	Steroids	Poor recovery
Haruna et al[17]	77, F	Pfizer-BioNTech, 2	2	Y	N	N	Normal	Neck	N	ESR: 100 mm/h; CRP: 43 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at the cervical and lumbar interspinous bursae, ischial tuberosities, trochanteric areas	Steroids	Improvement
Hussain et al[18]	65, F	AstraZeneca, 1	2	Y	Y	Y	↓	Small joint arthralgia	N	CRP: 105 mg/L	n/r	Steroids	Improvement
Izuka et al[19]	70, M	Moderna, 2	7	N	Y	Y	n/r	N	Headache, jaw claudication, and scalp tenderness	ESR: 75 mm/h; CRP: 151.4 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake around the bilateral shoulder joints, hip joints, greater trochanter interspinous bursa, and ischial tuberosity with no signs of temporal arteritis or large-vessel vasculitis; **USG:** Mild B/L biceps tenosynovitis.	Acetaminophen	Complete recovery
Lourenço et al[20]	75, F	AstraZeneca, 1	14	Y	Y	Y	↓ at hips and shoulders	Knees	N	ESSR: 120 mm/h; CRP: 80 mg/L	**USG:** Effusion on both shoulders, hips and knees.	Steroids	Improvement

(continued)

Table 1. (continued)

Authors	Age, sex	Vaccination		Clinical features						Inflammatory markers	Imaging	Treatment	Outcomes
		Vaccine, doses	Latency, d	Morning stiffness	Shoulder stiffness	Hip pain	Range of movement	Other joints involvement	GCA symptoms				
Manzo et al[21]	69, F	Pfizer-BioNTech, 1	1	Y	Y	Y	n/r	N	N	ESR: 105 mm/h; CRP: 750 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake in peri-articular and extra-articular synovial structures of shoulder and pelvic girdles	Steroids	Improvement
Mohareb et al[22]	76, M	AstraZeneca, 1	7	Y	Y	N	↓ shoulder abduction	Hand, PIP and MCP, knee and ankle	N	CRP: 96 mg/L	**USG:** B/L sub deltoid bursitis	Steroids	Improvement
Mohareb et al[22]	68, M	Pfizer-BioNTech, 1	14	Y	Y	N	↓ shoulder movement	Hand	N	CRP: 61 mg/L	**USG:** Findings of biceps tendonitis	Steroids	Improvement
Mohareb et al[22]	73, M	AstraZeneca, 1	7	N	N	Y	↓ shoulder movement	Neck, hands	N	CRP: 105 mg/L	n/r	Steroids	Improvement
Mohareb et al[22]	65, M	AstraZeneca, 1	7	Y	Y	Y	↓ shoulder movement	N	N	CRP: 161 mg/L	n/r	Steroids	Improvement
Osada et al[23]	80, F	Pfizer-BioNTech, 2	1	Y	Y	Y	↓ abduction of both shoulders	Neck, knees	N	ESR: 96 mm/h; CRP: 58.3 mg/L	**USG:** Effusion in the left subacromial bursa and around the long head of the biceps tendons bilaterally	Steroids	Improvement
Ottaviani et al[24]	70, F	Pfizer-BioNTech, 2	15	N	Y	Y	n/r	N	N	CRP: 224 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at shoulders, hips, interspinous, ischial tuberosities, sternoclavicular joints; **USG:** Long tendon of biceps involved, subacromial bursitis	Steroids	Improvement
Ottaviani et al[24]	74, F	Pfizer-BioNTech, 2	14	N	Y	Y	n/r	Neck, wrists	N	CRP: 34 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at Shoulders, hips, interspinous, ischial tuberosities, sternoclavicular joints; **USG**: Long tendon of biceps involved, subacromial bursitis	Steroids, MTX	Improvement

(continued)

Table 1. (continued)

Authors	Age, sex	Vaccination		Clinical features						Inflammatory markers	Imaging	Treatment	Outcomes
		Vaccine, doses	Latency, d	Morning stiffness	Shoulder stiffness	Hip pain	Range of movement	Other joints involvement	GCA symptoms				
Ottaviani et al[24]	77, F	Pfizer-BioNTech, 2	10	N	Y	Y	n/r	Neck, wrists	N	CRP: 32 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at Shoulders, hips, interspinous, ischial tuberosities, sternoclavicular joints.	Steroids	Improvement
Ottaviani et al[24]	65, M	Moderna, 2	10	N	Y	Y	n/r	Neck, wrists, knees	N	CRP: 34 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at Shoulders, hips, interspinous, ischial tuberosities, wrists; **USG:** Long tendon of biceps, glenohumeral joint involved, subacromial bursitis	Steroids, MTX	Improvement
Ottaviani et al[24]	78, F	Pfizer-BioNTech, 2	15	N	Y	Y	n/r	Wrists	N	CRP: 100 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at shoulders, hips, interspinous, ischial tuberosities, sternoclavicular joints, symphysis, wrists	Steroids	Improvement
Ottaviani et al[24]	73, F	Pfizer-BioNTech, 1	10	N	Y	Y	n/r	Wrists	N	CRP: 114 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at shoulders, hips, ischial tuberosities, sternoclavicular joints, symphysis, wrists; **USG:** Long tendon of biceps, wrist involved, subacromial bursitis	Steroids	Improvement
Ottaviani et al[24]	75, F	Pfizer-BioNTech, 2	5	N	Y	Y	n/r	Neck	N	CRP: 20 mg/L	**18 F-FDG PET/CT:** Increased FDG uptake at shoulders, hips, interspinous, ischial tuberosities, sternoclavicular joints, symphysis, wrists	Steroids	Improvement
Safary et al[25]	52, F	AstraZeneca, 2	14	Y	Y	Y	n/r	Neck	N	ESR: 65 mm/h; CRP: 36 mg/L	n/r	Steroids, MTX	Improvement

(continued)

Table 1. (continued)

		Vaccination		Clinical features									
Authors	Age, sex	Vaccine, doses	Latency, d	Morning stiffness	Shoulder stiffness	Hip pain	Range of movement	Other joints involvement	GCA symptoms	Inflammatory markers	Imaging	Treatment	Outcomes
Safary et al[25]	74, F	AstraZeneca, 1	24	Y	Y	Y	n/r	Neck	N	ESR: 77 mm/h; CRP: 36 mg/L	**USG:** B/L subacromial bursitis	Steroids	Improvement
Safary et al[25]	85, M	AstraZeneca, 1	1	Y	Y	Y	n/r	Neck	N	ESR: 97 mm/h; CRP: 26 mg/L	n/r	Steroids	Improvement
Vanni et al[26]	68, M	AstraZeneca, 1	20	Y	Y	N	↓ in upper limbs	N	N	ESR: 57 mm/h; CRP: 75 mg/L	**USG:** Left biceps tenosynovitis and right subacromial-subdeltoid bursitis	Steroids	Improvement
Vanni et al[26]	66, F	AstraZeneca, 1	45	Y	Y	N	↓ in upper limbs	Neck	N	ESR: 71 mm/h; CRP: 97 mg/L	n/r	Steroids	Improvement
Watad et al[27]	70, M	Pfizer-BioNTech, 1	3	N	Y	Y	n/r	N	N	ESR: 90 mm/h; CRP: 175 mg/L	n/r	Steroids	Improvement
Yamada et al[28]	67, M	Pfizer-BioNTech, 2	7	Y	Y	Y	↓ at shoulders and hips	Elbows, knees, wrists	N	CRP: 56 mg/L	**USG:** Bilateral biceps tenosynovitis	Steroids	Initial improvement; Developed GBS after 1 month
Yokote et al[29]	71, F	Pfizer-BioNTech, 1	10	Y	Y	Y	↓	Neck, shoulder and knee	Jaw claudication	ESR: 99 mm/h; CRP: 188 mg/L	**Gallium-67 scintigraphy** performed 72 hours after intravenous injection showed a B/L increased uptake in shoulders, hips, knees, ankles	Steroids	Improvement

Anti-CCP and Rh factor were negative in all cases. M, male; F, female; Y, symptom present; N, symptom absent; n/r, not reported; ↓, decreased; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CRP; C-reactive protein; USG, ultrasound; 18F-FDG PET/CT: 18F fluorodeoxyglucose positron emission tomography.

Table 2. Demographic characteristics and clinical features of cases reported as GCA following COVID vaccinations.

		Vaccination		Signs and symptoms							Confirmatory investigations			
Authors	Age, Sex	Vaccine received, doses	Latency period, d	New-onset temporal headache	Jaw claudication	PMR features	Scalp tenderness	Sudden visual loss	Temporal artery tenderness	Inflammatory markers	Temporal artery biopsy	Radiology	Treatment	Outcomes
Anzola et al[30]	83, F	Pfizer, 1	1	Y	N	N	Y	N	Y	ESR: 71 mm/h; CRP: 136 mg/L	Normal	**USG:** a noncompressible halo sign in the parietal branch of the right temporal artery; PET scan: an abnormal artery uptake suggestive of bilateral vertebral vasculitis	Steroids + Methotrexate	Remission
Arias et al[31]	71, F	Janssen, 1	4	Y	N	Y	N	N	N	ESR: 95 mm/h; CRP: 58.9 mg/L	Disruption of the internal elastic membrane and multinucleated giant cells.	**18FDG-PET/CT scan:** showing uptake foci in the aorta, supra-aortic trunks, shoulders, and hips.	Steroids	Resolution
Bounia et al[32]	71, F	Pfizer, 2	14	N	Y	Y	N	N	N	ESR: 117 mm/h; CRP: 50 mg/L	Presence of giant cells in the adventitia and media; disruption of the internal elastic lamina.	**FDG PET scan:** Increased uptake in the subclavian arteries along with a less marked increase of FDG uptake in the thoracic and the abdominal aorta and the right common iliac artery	Steroids	Resolution
Cadiou et al[15]	70, F	AstraZeneca plus Moderna, 1	10	N	N	Y	N	N	N	CRP: 104 mg/L	n/r	**PET-CT:** pan aortic and supra-aortic vasculitis.	Steroids	Improvement
Cadiou et al[15]	74, F	Pfizer, 1	7	Y	Y	N	Y	N	N	CRP: 190 mg/L.	Granuloma and fragmentation of the internal elastic lamina.	n/r	Steroids	Improvement
Che et al[33]	87, F	Pfizer	1	N	N	N	Y	Y	N	ESR: 120 mm/h; CRP: 8.2 mg/l	Biopsy of right temporal artery confirmed GCA	n/r	Steroids	Visual symptoms worsened.
Dhungana et al[34]	66, F	AstraZeneca	6 hrs	Y	N	N	Y	N	Y	CRP: 16.8 mg/L	n/r	**Post corticosteroid USG:** normal temporal artery	Steroids	Improvement
Dhungana et al[34]	70, M	AstraZeneca	1	Y	Y	N	Y	N	Y	ESR: 38 mm/h; CRP: 25.5 mg/L	n/r	**USG:** Halo in frontal branch of right temporal artery.	Steroids	Improvement

(continued)

Table 2. (continued)

		Vaccination		Signs and symptoms							Confirmatory investigations			
Authors	Age, Sex	Vaccine received, doses	Latency period, d	New-onset temporal headache	Jaw claudication	PMR features	Scalp tenderness	Sudden visual loss	Temporal artery tenderness	Inflammatory markers	Temporal artery biopsy	Radiology	Treatment	Outcomes
Gilio et al[35]	63, F	Pfizer, 1	5	Y	N	Y	N	N	N	ESR: 104 mm/h; CRP: 74 mg/L	n/r	**PET scan:** increased FDG uptake by large arteries and the distribution of vasculitis with large artery (aortic arch, thoracic and abdominal aorta) involvement of carotid, subclavian arteries suggest large-vessel vasculitis.	Steroids	Resolution
Greb et al[36]	79, M	mRNA vaccine, 2	2	Y	N	N	Y	Y	N	ESR: 97 mm/h; CRP: 272 mg/L	Patchy intramural inflammatory infiltrates composed of lymphocytes and rare multinucleated giant cells at the internal lamina and adventitia consistent with a diagnosis of GCA.	n/r	Steroids	Resolution
Ishizuka et al[37]	74, M	Pfizer, 3	1	Y	N	N	N	N	N	ESR: 79 mm/ h; CRP: 63.2 mg/l	n/r	**PET/CT:** Hyperaccumulation in the thoracic aorta, subclavian, axillary, brachial and temporal arteries/	Steroids	Improvement
Mejren et al[38]	62, F	Pfizer, 2	21	N	N	N	N	N	N	CRP: 98 mg/L	n/r	**USG:** Segmental hypoechoic wall thickening of the axillary arteries bilaterally; **PET scan:** Moderate-to-high FDG uptake in the vertebral, maxillary, subclavian, common carotid, axillary, internal mammary and the proximal part of the common iliac arteries bilaterally and throughout the aorta.	Steroids	Improvement

(continued)

Table 2. (continued)

		Vaccination		Signs and symptoms							Confirmatory investigations			
Authors	Age, Sex	Vaccine received, doses	Latency period, d	New-onset temporal headache	Jaw claudication	PMR features	Scalp tenderness	Sudden visual loss	Temporal artery tenderness	Inflammatory markers	Temporal artery biopsy	Radiology	Treatment	Outcomes
Lo Sardo et al[39]	78, M	AstraZeneca, 2	1	Y	Y	N	N	N	N	CRP: 83.9 mg/L	Transmural inflammatory infiltrate with giant cells, compatible with giant cell arteritis	**FDG-CT PET:** evidence of active large-vessel vasculitis with abnormal artery uptake at the level of the ascending aorta, aortic arch (SUV max 4.2), descending aorta, iliac axes bilaterally and subclavian bilaterally.	Steroids + Tocilizumab	Resolution
Sauret et al[40]	70, M	AstraZeneca, 1	Few days	Y	N	N	N	N	N	CRP: 5.0 mg/L	Intima thickening, fragmentation of internal elastic lamina, and moderate infiltration of the media with giant cells.	**PET scan, CT:** Unremarkable.	Steroids	Resolution
Shi et al[41]	67, F	AstraZeneca	4	N	N	N	N	N	N	ESR: 127 mm/h; CRP: 168 mg/L	n/r	**USG:** No halo or stenosis in temporal artery; **PET scan:** Significant uptake in the ascending thoracic aorta, both internal carotid arteries and subclavian artery, suggestive of a large-vessel vasculitis.	Steroids, followed by Methotrexate, tocilizumab	Improvement
Ursini et al[42]	78, M	AstraZeneca	1	Y	Y	N	N	N	N	n/r	Findings consistent with inflammation of the vessel wall and the presence of giant cells	**PET/CT scan:** 18F-FDG accumulation in proximal aorta	Steroids	Active disease at follow-up after 3 weeks
Ursini et al[42]	82, F	Moderna	8	Y	N	N	N	Y	Y	n/r	n/r	n/r	Steroids	Remission
Ursini et al[42]	67, F	AstraZeneca	14	N	Y	N	N	N	N	n/r	n/r	**USG:** showed the typical "halo" sign	Steroids	Remission
Wakabayashi et al[43]	77, M	Pfizer, 3	1	Y	N	N	Y	N	Y	ESR: 62 mm/h; CRP: 134 mg/L	Normal	**USG**: a halo sign surrounding the bilateral temporal arteries	Steroids + Tocilizumab	Resolution
Xia et al[44]	68, M	AstraZeneca, 2	4	Y	Y	N	N	Y	N	ESR: 4 mm/h; CRP: 29 mg/L	Temporal artery biopsy confirmed GCA diagnosis.	n/r	Steroids + Tocilizumab after recurrence	Recurrence

M, male; F, female; Y, symptom present; N, symptom absent; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; USG, ultrasound; FDG-CT PET, fluorodeoxyglucose 18 positron emission tomography.

Table 3. Comparison of findings in cases with COVID vaccination-associated giant cell arteritis and polymyalgia rheumatic.

Parameter	GCA		PMR	
Cases	20		30	
Age (mean)	72.85 ± 6.82 y		71.06 ± 6.14 y	
F: M ratio	12:8 (1.5)		18:12 (1.5)	
Vaccine administered, No. (%)	AstraZeneca	9 (45%)	10 (33.3%)	
	Pfizer	8 (40%)	16 (53.3%)	
	Moderna	1 (5%)	3 (10%)	
	Others	2 (10%)	1 (3.3%)	
Latency (mean)		5.3 ± 5.62 days	11.03 ± 8.89 days	
Symptoms, No. (%)	Headache	14 (70%)	Morning stiffness	17 (56.7%)
	Jaw Claudication	7 (35%)	Shoulder pain	28 (93.3%)
	Scalp tenderness	7 (35%)	Hips pain	24 (80%)
	Visual symptoms	4 (20%)	Decreased range of motion	12 (40%)
	PMR symptoms	4 (20%)	GCA symptoms	3 (10%)
ESR, No. (%)	Raised	10 (50%)	15 (50%)	
	Normal or not reported	10 (50%)	15 (50%)	
CRP, No. (%)	Raised	17 (85%)	29 (96.7%)	
	Normal or not reported	3 (15%)	1 (3.3%)	
Treatment, No. (%)	Steroids	20 (100%)	29 (96.7%)	
	Methotrexate	2 (10%)	3 (10%)	
	Tocilizumab	4 (20%)	0	
Outcomes, No. (%)	Favorable	18 (90%)	29 (96.7%)	
	Poor	2 (10%)	1 (3.3%)	
	Relapse	1 (5%)	1 (3.33%)	

Favorable outcomes, including complete or partial recovery, were reported in 96% of patients with PMR and 90% of patients with GCA. Relapse was reported in 1 patient with GCA post ChAdOx1 nCoV-19 vaccine, a viral vector vaccine.[44] The patient initially came with an atypical presentation with a normal ESR and slightly raised CRP. Moreover, relapse was reported in 1 patient with PMR. Despite initial symptom resolution with corticosteroid tapering, she experienced 2 flares, presenting with jaw claudication and scalp tenderness, both requiring methylprednisolone for symptom control. Although she had features suggestive of GCA, including jaw claudication and a temporal headache, her temporal artery biopsy was negative, and her disease course was dominated by PMR symptoms with a steroid-responsive relapsing pattern. This led to a diagnosis of PMR with possible temporal arteritis rather than definite GCA.[14]

Discussion

Our systematic review indicates that in predominantly older adults, especially females, COVID-19 vaccination is temporally associated with the onset of PMR and GCA, with most cases responding favorably to corticosteroid therapy, though causality remains unproven. Over time, certain manifestations associated with COVID-19 vaccination continue to evolve or become more apparent, potentially revealing both short-term and long-term effects that were previously unknown. Beyond the classical musculoskeletal manifestations, COVID-19 infection and vaccination may produce systemic and accessory symptoms such as fever, fatigue, malaise, headache, myalgia, arthralgia, and even neurological signs like tingling, burning sensations, and brain fog features that have been associated with small-fiber neuropathy in recent reports.[46] Included in the list of its immune-mediated manifestations are 2 closely related disorders, that is, PMR and GCA. Polymyalgia rheumatica and GCA are inflammatory conditions of periarticular structures and blood vessels, respectively, that have a largely unknown etiology, and often require corticosteroid and immunosuppressant therapy for managing symptoms and preventing complications.[47] Given the excessive rise in cases of these disorders after COVID-19 vaccination, early recognition of this clinical association is crucial to improve prognosis. This systematic review identifies demographic characteristics associated with GPSD and quantifies the most common clinical manifestations in patients diagnosed with COVID-19 vaccine-related PMR or GCA. This will help keep practicing physicians updated on these emerging manifestations while offering critical guidance for optimizing patient care.

Polymyalgia rheumatica and GCA have been associated with various immunizations, including but not limited to influenza and respiratory syncytial virus vaccines.[48-51] In one cohort study on causes of PMR, 39% of participants reported that infection or vaccination had a temporal association with PMR, indicating a potential association.[52] This association can be physiologically plausible considering the immune system's heightened response to vaccination, on the one hand, and the involvement of both innate and adaptive immunity in the pathophysiology in the case of PMR and GCA.[53,54] Elevated levels of pro-inflammatory

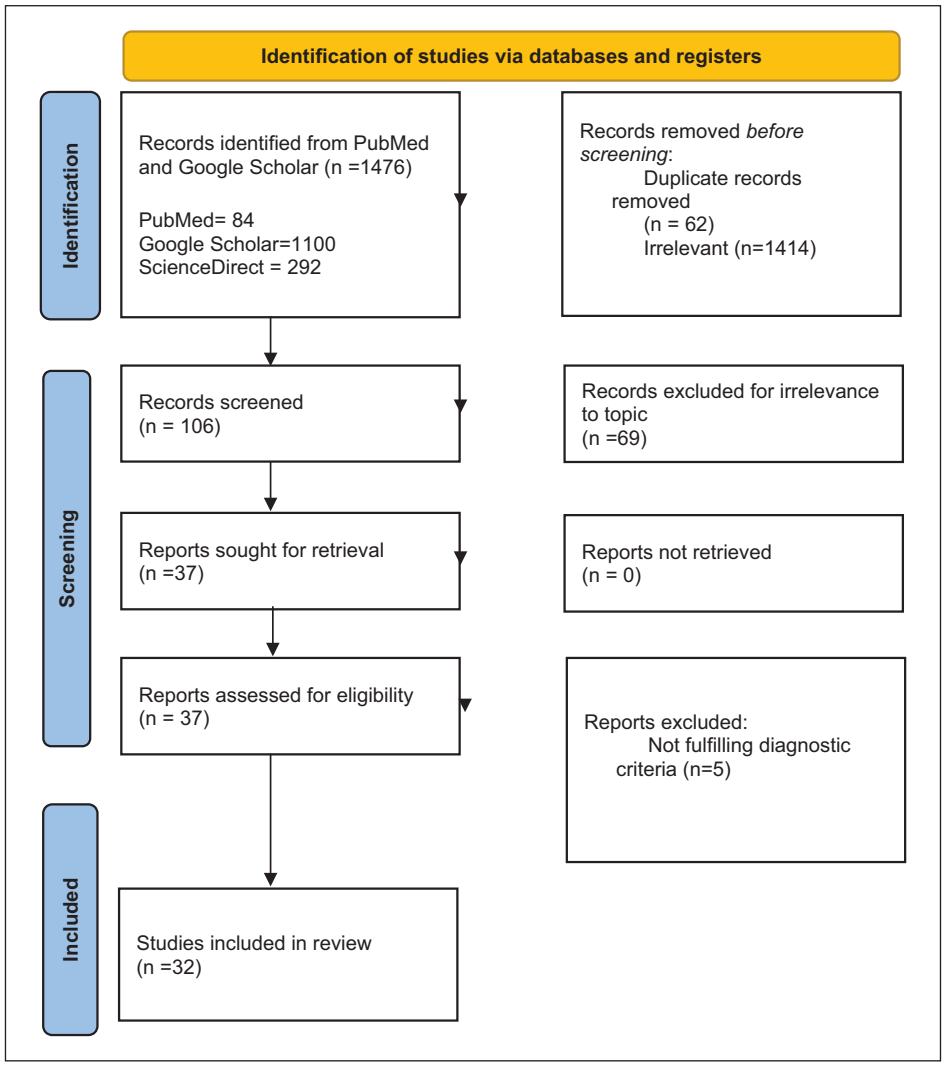

Figure 1. PRISMA 2020 flow diagram for study selection.

cytokines, such as IL-1 and IL-6, are central to the inflammation seen in PMR and GCA. Immune cell activation, thus, is a key feature of the pathophysiology of GPSD, with T cells and macrophages playing vital roles.[55] In the case of mRNA-based COVID vaccines, the translated spike protein activates antigen-presenting cells and stimulates the activation of cytokine as part of an adaptive immune response.[56] The underlying mechanism of both is hence quite similar. While the excessive cytokine production contributes to the inflammation and tissue damage in GPSD, a similar but heightened cytokine production with COVID-19 vaccines orchestrates an immune response against COVID-19. Another potential explanation for the association between GPSD and COVID-19 vaccination is the "molecular mimicry hypothesis." The spike protein of the SARS-CoV-2 virus, which the vaccines emulate, might share epitopes with proteins in vascular or musculoskeletal tissues, leading to an immune-mediated response in predisposed individuals.[57] Supporting this hypothesis, recent data have suggested that specific HLA alleles, including HLA-DRB1*11 and HLA-C*07, may confer genetic susceptibility to aberrant immune activation after vaccination. Furthermore, biomarkers such as IL-6 and calprotectin commonly elevated in PMR and GCA have also been reported in postvaccine cases, reinforcing the biological plausibility of this association.[58] However, further research is needed to elucidate the exact pathophysiological pathways involved.

We pooled the incidence of 30 PMR and 20 GCA cases occurring after COVID-19 vaccination. Patient demographics were similar to usual cases of PMR having a mean age of 72.85 years with a female preponderance, and cases of GCA having a mean age of 72.85 years also with a slight female dominance. Another cohort concluded the same point that de novo cases and post-COVID-19 vaccination cases of PMR were similar in presentation and prognosis.[59] This is in contrast to immune checkpoint mediators–induced PMR and GCA cases which have a distinct clinical profile than de novo disease.[60] Administration of Pfizer-BioNTech (48%), an mRNA-based vaccine, and AstraZeneca (38%), a viral vector-based vaccine, were most commonly associated with postvaccine GCA or PMR. The higher proportion of cases involving Pfizer-BioNTech and AstraZeneca vaccines may reflect their overall distribution in the studied populations rather than an increased risk of PMR or GCA associated specifically with these

vaccines. The latency period from vaccine administration to causation was 11.03 and 5.3 days for PMR and GCA, respectively. This aligns with the findings of Mettler et al,[61] which also report a median (interquartile range) time of 4 (1-14) days from vaccination to the onset of the first symptoms of GCA, PMR, or a combination of both. This latency period is comparable to the time needed to reach a peak immune response after vaccine administration, as indicated by the 95% vaccine efficacy observed starting at least 7 days after the second dose.[62] Prognosis was generally good and most patients treated with corticosteroid therapy reported excellent symptom control. Continued management was essential in a subset of patients who experienced relapse. However, it is important to note that very few patients were followed in the long term and reported numbers, hence, could be seriously under-representative of actual outcomes.

The findings of this review align with previous literature on vaccine-related occurrences or exacerbations of immune-mediated diseases.[63-66] However, these associations are often difficult to establish due to the limited number of clinical trials and low incidence of such events compared with the high prevalence of vaccinations.[67,68] Furthermore, the temporal association does not necessarily imply causation. Several studies have suggested that the overall risk of developing PMR or GCA following vaccination is extremely low.[9,61] It is also important to note that there is an increased risk of immune-mediated diseases with COVID-19 infection itself, which has been shown to trigger or worsen various immune-mediated conditions.[69,70] Our systematic review documented 50 cases of postvaccination PMR and GCA, which—when compared with background incidence rates reported in the literature—appear to fall within the expected range for these conditions in older adults. For instance, studies report GCA incidence rates ranging from 1.1 to 43.6 per 100 000 (with higher rates in Northern Europe and Minnesota), while PMR rates are generally higher. This comparison suggests that the observed cases might largely reflect the underlying background incidence rather than a vaccine-specific effect, emphasizing the need for ongoing pharmacovigilance to accurately monitor these rare events.[71] Thus, the review underscores the importance of continued vaccination efforts, particularly in older adults who are at increased risk of both COVID-19 complications and PMR/GCA and emphasizes the careful selection of individuals for vaccination, especially those with a history of or current GCA, PMR, or other immune-mediated disorders, to identify those at higher risk for vaccine-related adverse events.

There are limitations to this work. Our review relies entirely on case reports and case series, which do not represent all instances of PMR or GCA following COVID-19 vaccination and are prone to bias and confounding factors. Subsequently, quantitative pooling of results via a meta-analysis could not be performed as the available evidence consisted solely of case reports and small case series with significant variability in diagnostic testing, follow-up duration, and reporting of outcomes. In addition, the lack of standardized criteria for diagnosing vaccine-related PMR/GCA exacerbations makes it challenging to draw definitive conclusions. We employed the 2012 EULAR criteria for PMR and the 2022 criteria for GCA diagnosis that may have excluded studies that used older or purely clinical diagnostic methods. Although these criteria were selected to enhance consistency and diagnostic precision, their application may have limited the scope of the review. The issue of unreported cases raises concerns about the applicability of the current findings to the broader population. In addition, the results showed inherent variability due to differences among individual patients and the subjective nature of case reporting by physicians. For instance, there was significant heterogeneity in terms of the latency period each study used to define GCA and PMR which may have included patients not temporally compatible with vaccine-triggered disease. The lack of a universally accepted latency threshold limits the ability to establish temporal cause-effect relationship in this review and highlights the need for standardization. Despite these challenges, the rigorous methodology employed for literature searching and data extraction supports the robustness of our comprehensive review of the clinical and pathophysiological aspects of PMR/GCA. Future research should focus on large-scale epidemiological studies and mechanistic research to better understand the relationship between COVID-19 vaccination and immune-mediated diseases.

Conclusions

A temporal association exists between COVID-19 vaccination and the onset or flare of PMR and GCA. However, causality remains unproven. Disease manifestations are similar to normal disease processes and most patients respond well to steroid treatment. Larger studies are vital to further explore this potential association.

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Consent for Publication

The authors ensured that consent had been obtained from patients for the original publication of their cases.

Author Contributions

FS: Conceptualization, Supervision, Project administration, Investigation, Formal analysis, Data curation, Writing—original draft, review & editing, Revision. HF: Writing—original draft, Methodology, Revision. HA: Writing—review & editing, Writing—original draft, Methodology. GMM: Writing—review & editing, Writing—original draft, Methodology, Data curation.

HS: Writing—review & editing, Validation. MZA: Methodology, Validation. LF: Writing—review & editing, Writing—original draft. FA: Methodology. ZA: Writing—review & editing, Writing—original draft, Methodology. TZA: Writing—original draft, Writing—review & editing. GR: Data curation. AR: Conceptualization, Writing—review & editing.

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