



## Giant Cell Arteritis after COVID-19 Vaccination along with Immuno-Pathogenesis of this Entity

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### ABSTRACT

The previous report described the new-onset autoimmune phenomena following COVID-19 vaccine, suggesting that the molecular mimicry, autoantibodies production, and the certain vaccine adjuvants contribute to induce the autoimmune phenomena. Giant Cell Arteritis (GCA) is regarded as the autoimmune and auto-inflammatory disease and some reports of GCA after COVID-19 vaccine have been provided. The recent report has described the generalized morphea after COVID-19 vaccination along with characteristic nature of spike protein, suggesting that the development of severe type may be attributed to the molecular mimicry along with IFN-1 immune response. In this article, current knowledge and trends of GCA after COVID-19 vaccination along with immune-pathogenesis of GCA have been reviewed. Regarding immune-pathogenesis for GCA, the abnormal immune response derived from aged immune system and altered aging vascular status such as senescent endothelial cell and vascular smooth muscle cell may contribute to induce the development of GCA. The result provided that all patients showed the positive findings of halo sign on ultrasound or temporal artery biopsy described in the 2022 American College of Rheumatology/EULAR classification criteria for GCA. The development of GCA following COVID-19 vaccination may be attributed to the molecular mimicry along with IFN-1 immune response in old predisposed individuals.

**Keywords:** COVID-19 vaccination; Giant cell arteritis; Molecular mimicry; IFN-1; Immunopathogenesis of giant cell arteritis

### INTRODUCTION

Chen et al. suggested that the molecular mimicry, autoantibodies production, and the certain vaccine adjuvants contribute to induce the autoimmune phenomena after COVID-19 vaccine [1]. GCA is considered as the autoimmune and auto-inflammatory disease and some reports of GCA after COVID-19 vaccination have been provided [2,3]. The recent report has described the generalized morphea after COVID-19 vaccination along with characteristic nature of spike protein, suggesting that the development of severe type may be attributed to the molecular mimicry along with IFN-1 immune response [4]. With respect to the adverse effects after COVID-19 vaccination, the trends of molecular medicine suggested that the characteristic aspects of the spike protein itself either due to molecular mimicry with human tissues or as an ACE2 ligand

may cause the mRNA vaccination-mediated adverse effects such as an autoimmune disease [5]. The study described the adverse effects after COVID-19 vaccination which may associate with a pro-inflammatory behavior of the lipid nanoparticles contained [5]. Additionally, it is known that IFN-1 induced by COVID-19 mRNA and adenovirus vector vaccines may also produce inflammatory and cytotoxic mediators, and CD4<sup>+</sup> T follicular helper cells [6]. Regarding immune-pathogenesis of GCA, the study provided that immune system damaged blood system suggesting the three phases of pre-GCA period, vessel wall invasion, and progressive tissue destruction [7]. The 2022 American College of Rheumatology/EULAR classification criteria for GCA including clinical, laboratory, imaging, and biopsy criteria have been provided [8]. In this article, current knowledge and trends of GCA

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after COVID-19 vaccination along with immune-pathogenesis of GCA have been reviewed.

## LITERATURE REVIEW

### Adverse effects after COVID-19 vaccination

The previous report described the new-onset autoimmune phenomena following COVID-19 vaccine including immune-mediated thrombotic thrombocytopenia, autoimmune liver disease, Rheumatic Arthritis (RA), suggesting that the molecular mimicry, autoantibodies production, and the action of vaccine adjuvants contribute to induce the autoimmune phenomena [1]. Some reports of GCA after COVID-19 vaccine have been described [3]. The recent report has described the generalized morphea after COVID-19 vaccination along with characteristic nature of spike protein, suggesting that the development of severe type may be attributed to the molecular mimicry along with IFN-1 immune response [4]. The mRNA-1273 vaccine is a lipid nanoparticle-encapsulated mRNA-based vaccine manufactured by Moderna [9] and the BNT162b2 mRNA is a lipid nanoparticle formulated nucleoside-modified RNA vaccine manufactured by Pfizer-BioNTech [10]. Meanwhile, the Ad26.COV2.S is a human Adenovirus type 26 vectored vaccine manufactured by Jansen/Johnson and Johnson [11]. The recent study by Roltgen et al. provided that mRNA vaccination was related to follicular hyperplasia including the induction of Germinal Centers (GCs) B cells, T follicular helper (Tfh) cells, and follicular dendritic cell networks showing a prolonged presence of vaccine mRNA in Lymph Nodes (LNs) GCs and spike antigen in LN GCs and blood [12]. It is known that the mRNA used in mRNA vaccine represents both antigen and adjuvant leading to induce inflammation and immunity response [6]. Trougakos et al. described the adverse effects after vaccination which may associate with a pro-inflammatory behavior of the lipid nanoparticles contained [5]. The trends of molecular medicine suggested that the characteristic aspects of the spike protein itself either due to molecular mimicry with human tissues or as an ACE2 ligand may cause the mRNA vaccination mediated adverse effects such as an autoimmune disease [4,5]. Additionally, it is known that IFN-1 induced by COVID-19 mRNA and adenovirus vector vaccines may also produce inflammatory and cytotoxic mediators, and CD4<sup>+</sup> T follicular helper cells [4,6].

### Primary systemic vasculitides

Regarding Primary Systemic Vasculitides (PSV) including small, medium, and large vessels, due to the response to local vessel wall inflammation, the progression of both atherosclerosis and arteriosclerosis status have been suggested [13,14]. The mechanisms of vascular wall inflammation included endothelial dysfunction, autoantibody-mediated or associated vascular damage, immune complex formation and complement activation [15]. Evidence showed accelerated atheromatosis (atherosclerosis) and arterial stiffening in patients with PSV including large vessel such as GCA and Takayasu Arteritis (TA) [16]. According to the 2012 revised international Chapel hill consensus conference nomenclature of vasculitides, Large-Vessel

Vasculitis (LVV) can be classified into GCA and TA [15]. GCA is the most common form of PSV in patients aged >50 years involving large and medium sized vessels for the cranial arteries derived from the carotid artery while TA occurs in patients under 50 years [15,17]. The author previously described a few case reports of Takayasu Arteritis (TA) and a review article of TA focusing on Common Carotid Artery (CCA) features such as macaroni sign on gray-scale Ultrasonography (US) and Peak Systolic Velocity (PSV) levels reflecting inflammatory status on CCA by pulsed and color Doppler US [18-20]. With respect to the inflammatory process in GCA, the report described that the transmural inflammatory infiltrations including lymphocytes, macrophages, and giant cells are pathologically ordinary aspects in GCA, representing a concentric rings feature, with a thicker inflammatory band [21]. Similar to Takayasu Arteritis, it is known that the inflammatory process in GCA begins from the adventitial layer at the level of the vasa vasorum and progresses to the media, leading to affect all layers of the arterial walls [16]. Weyand et al. also described that T cells, mostly CD4<sup>+</sup> T cells and monocyte/macrophages that form the granulomatous lesions in GCA involved arteries invade the adventitia from vasa vasorum and affect the media and intima [7]. Following a prolonged period of asymptomatic autoimmunity, the loss of tissue tolerance and vessel wall invasion of the immune cells leads to establish granulomatous lesions. In result, vaso-occlusion, wall dissection, and aneurysmal formation have been established [7].

### Classification criteria for giant cell arteritis

Based on the 2012 revised international Chapel hill consensus conference nomenclature of vasculitides, Large-Vessel Vasculitis (LVV) can be classified into GCA and TA [15]. GCA is generally known as a disease vasculitis affected of the cranial region, particularly the temporal arteries with an age >50 years at time of diagnosis [15]. It has been suggested that the ACR 1990 criteria for GCA focus on cranial aspects of GCA and do not perform well in patients with large vessel vasculitis [8,22]. 2022 American college of rheumatology/EULAR classification criteria for GCA has been developed, indicating that these classification criteria should be applied to classify the patients as having giant cell arteritis when a diagnosis of medium vessel or large vessel vasculitis has been established. The new classification criteria for GCA included age >50 years at time of diagnosis, additional clinical criteria such as sudden visual loss, laboratory, imaging and biopsy criteria such as positive findings of temporal artery biopsy or halo sign on temporal artery ultrasound. The new classification criteria indicated that a cut-off of >6 points is needed for the classification of GCA. A cut-off of >6 points in total risk score in the validation data set showed that the sensitivity was 87.0% and specificity was 94.8%. And the area under the curve for the model was 0.91 [8]. Molina-Collada et al. noted that the new criteria had a sensitivity of 92.6% and a specificity of 71.8% respectively suggesting that 2022 ACR/EULAR GCA classification criteria exhibited an improvement on the sensitivity and specificity of the 1990 ACR classification criteria [23].

## Halo sign on temporal artery US in giant cell arteritis

It is known that US can replace temporal artery biopsy to diagnose GCA. For the patients with cranial GCA, if US study is not available or US examinations are not conclusive, CT, MRI and PET-CT examinations can be used as an alternative diagnostic procedure [17]. New 2022 ACR/EULAR suggested that positive findings of temporal artery biopsy or halo sign on temporal artery ultrasound showed 5 points. Regarding the transducer frequency of the temporal artery ultrasound, some studies have been provided [24-26]. Ponte et al. also suggested the halo sign is diagnostic and follow-up markers for disease activity following therapeutics [27]. OMERACT has defined the halo sign as a thickened homogeneous, hypo echoic wall well delineated towards the luminal side, exhibiting the US appearances of active phase in GCA [28]. It is important that the halo sign is observed both in longitudinal and transverse views, while the compression sign is also examined to confirm the presence of a halo [28,29]. The inflammatory thickness is not compressible using the pressure with the probe and this finding has been termed the compression sign [29]. It is suggested that the halo and the compression signs are considered as the most important abnormalities on US for GCA using the consensus-based definition [30]. The previous report suggested that cut-off levels for intima-media thickness of temporal, fascial, and axillary arteries can assist with regard to diagnosis and follow-up studies for GCA [31]. The author suggested that the US test by high resolution frequency probe used in dermatology is needed to detect/diagnose for GCA due to the superficial location of temporal artery. As temporal artery is anatomically branched from External Carotid Artery (ECA), similar to the previous reports in TA, the author recommends the examination of the Peak Systolic Velocity (PSV) levels on ECA reflecting inflammatory status by pulsed and color Doppler US [18-20].

## FDG-PET procedure

FDG-PET (Fluorodeoxyglucose-Positron Emission) procedure is an established form of molecular image use to diagnose disease and monitor therapeutics response in oncology field [32]. We previously studied the PET imaging for oncology [33]. Meanwhile, it is known that activated inflammatory cells show increased glycolytic activity similar to certain tumor cells, thereby this procedure is the potential usefulness to evaluate the inflammation status [32]. Atherosclerosis is low grade and chronic arterial inflammatory status and endothelial dysfunction evaluated by FMD and NMD examination is the initial step in atherosclerosis [34-36]. PET procedure has been also used to estimate the atherosclerosis state [37]. Concerning long COVID-19, the author described the arterial stiffness in COVID-19 along with persistent inflammatory process [38]. The previous report described the vacuities changes in COVID-19 survivors with sustained manifestations using FDG-PET/CT study [39,40]. According to the previous report, FDG-PET is useful to evaluate the presence of LVV-GCA for early vascular inflammation in comparison with MRI or CT and two meta-analyses have demonstrated the diagnostic performance of PET or PET/CT in GCA [17]. Recent FDG-PET/CT study by

Deauville criteria also showed a standardized score for the diagnosis of GCA [41]. The new classification criteria stated the abnormal FDG uptake in the arterial wall throughout the descending thoracic and abdominal aorta on PET as the activity for LVV-GCA [8].

## Immuno-pathogenesis of giant cell arteritis

It is known that GCA is a granulomatous lesion showing the inflammatory infiltrates within the vessel wall layers. The media and intima are occupied by the CD4<sup>+</sup> T cells and macrophages whereas the adventitia is affected by lymphocyte, infrequently multinucleated giant cells leading to a maladaptive remodeling status [42]. It is known that CD4 T helper 1 (TH1) and TH17 cells invade into the vessel wall of the aorta and large elastic arteries [43]. Regarding the performance of immune regulatory functions, Wen et al. described that adventitial micro vascular Endothelial Cells (mvECs) up-regulate the expression of the NOTCH ligand Jagged 1. The study provided that VEGF induced the Jagged 1 expression leading to mvECs to regulate effector T cell induction *via* the Notch-mTORC1 pathway [43]. It is suggested that the interaction between T-cell and endothelial cell leads to leakiness of the micro vascular basement membrane while the aberrant expression of Matrix Metalloprotease (MMP)-9 in circulating monocytes affects the incoming T cells and macrophages in patients with GCA [42]. With respect to the immuno-pathogenesis of giant cell arteritis, a link between loss of self-tolerance in the adaptive immune system and aberrant signaling in the NOTCH pathway leads to expansion of NOTCH1<sup>+</sup>CD4<sup>+</sup> T cells and the reduction of NOTCH4<sup>+</sup> T regulatory cells. Regarding vessel wall invasion process, a defect in the endothelial cell barrier of adventitial layer at vasa vasorum induces the invasion of monocytes, macrophages, and T cells into the arterial wall. In result, vasculitis with granulomatous inflammation is induced by the breakdown of the PD-1(Programmed cell Death protein 1)/PD-L1 (Prolonged cell Death Ligand 1) pathway [7].

## Interrelationship among GCA, aging immune and aging vascular status

According to the recent report, T cell aging as a risk determinant for autoimmunity includes RA and GCA. It is known that GCA patient broaden the pathogenic CD4<sup>+</sup> T cells due to the aberrant expression of the NOTCH1 and the loss of the PD-1/PD-L1 immune checkpoints. Additionally, patients with GCA decrease the anti-inflammatory Treg cells leading to the destructive granulomatous vacuities [44]. It is known that the aging immune systems tend to behave more inflammatory and more auto reactive, suggesting that the chronic low grade inflammation related to immune cell age is considered as Inflammageing [2]. Regarding vascular aging, senescent Endothelial Cell (EC) and Vascular Smooth Muscle Cell (VSMC), namely atherosclerosis process show the alteration of the interaction with immune cells [45]. It is plausible that abnormal immunity response derived from aged immune system and aged vascular status such as senescent EC and VSMC have been suggested in GCA, showing the decreased anti-inflammatory CD8<sup>+</sup> T regulatory cells [2]. The development of GCA may be attributed to the aberrant immune

response derived from aged immune system and age related changes in blood vessels.

### Giant cell arteritis following COVID-19 vaccination

It is known that the new onset or flare of autoimmune disease post-COVID-19 vaccine has been reported [3,46]. The pharmacovigilance study by Mettlers et al. indicated the risk of GCA and Polymyalgia Rheumatica (PMR) and also described the risk of systemic vasculitis following mRNA COVID-19 vaccination [47,48]. The result showed that the COVID-19 vaccinations were related to the increased reports in GCA and PMR, suggesting a decreased relative risk of GCA or PMR after COVID-19 vaccine, in comparison with influenza vaccine [47]. Anzola et al. reported a case of GCA after the first dose of COVID-19 mRNA vaccine (Pfizer/BioNTech) showing abnormal examination of the temporal artery, elevated ESR and CRP levels, non-compressible halo sign in the right parietal branch of the right temporal artery on US, and a suggestive of bilateral vertebral vasculitis on FDG-PET/CT scan [49]. In a dermatologic field, Gambichler et al. reported a case of GCA clinically almost complete vision loss, elevated CRP, and pathologically diagnosed bilateral late phase GCA after the second dose of COVID-19 vaccination (BTN162b2) [50]. The report by Sauret et al. described a case of GCA with HLA-DR4 after the first dose of COVID-19 vaccine (AZD1222), showing the diagnostic confirmation on temporal artery biopsy [51]. The recent report suggested that COVID-19 vaccines may induce platelet factor 4 antibody-mediated thrombotic thrombocytopenia [52]. Kaulen et al. reported a case of GCA based on patient age (>50 years), new onset of localized headache, temporal artery tenderness, and halo sign on US [53]. Greb et al. reported a case of GCA after the second dose of COVID-19 vaccination (mRNA) based on the myalgias, elevated CRP and ESR, and bilateral temporal artery biopsies [54]. Gilio et al. reported a case of large-vessel vasculitis presenting with PMR like symptoms, high ESR and CRP levels, and involved carotid and subclavian arteries on FDG-PET suggesting a diagnosis of LVV after COVID-19 vaccine (Pfizer/BioNTech) [55]. The recent report

described a case of GCA, showing the abnormal examinations of the temporal artery, elevated CRP, and halo sign on US after the third dose of COVID-19 vaccine (Pfizer/BioNTech) [56]. Sardo et al. described a new onset of GCA after COVID-19 vaccine (AstraZeneca) showing temporo-parietal headache, jaw claudication, elevated CRP, pathological features of temporal artery biopsy, and active LVV findings on FDG-PET/CT [57].

## DISCUSSION

It is known that T cells, mostly CD4<sup>+</sup> T cells and monocyte/macrophages that form the granulomatous lesions in GCA invade the adventitia from vasa vasorum and affect the media and intima [7]. Regarding immuno-pathogenesis of GCA, the study revealed that immune system damaged blood system suggesting the three processes of pre-GCA period, vessel wall invasion, and progressive tissue destruction. It is known that a link between loss of self-tolerance in the adaptive immune system and aberrant signaling in the NOTCH pathway leads to expansion of NOTCH1<sup>+</sup>CD4<sup>+</sup> T cells and the reduction of NOTCH4<sup>+</sup> T regulatory cells. Regarding vessel wall invasion process, a defect in the endothelial cell barrier of adventitial layer at vasa vasorum networks induces the invasion of monocytes, macrophages, and T cells into the arterial wall. In result, vasculitis with granulomatous inflammation is induced by the breakdown of the PD-1/PD-L1 pathway [7]. It is plausible that abnormal immune response derived from aged immune system and altered aging vascular status such as senescent EC and VSMC have been suggested in GCA, thereby the development of GCA may be attributed to the abnormal immune response and aging vascular status. The reports of GCA after COVID-19 vaccine with detailed findings are bibliographically shown in Tables 1 and 2. The new 2022 ARC/EULAR classification criteria for GCA provided that the halo signs on US or TA biopsy showed 5 points. The result provided that the positive findings of halo sign on US or TA biopsy have been shown in all patients (Table 1).

**Table 1:** GCA following COVID-19 vaccine (Imaging and Biopsy procedures).

Study	Age/sex	Halo sign on US or TA biopsy	FDG-PET
Anzola et al.	83/f	Halo sign	FDG-PET/CT
Gambichler et al.	82/m	Biopsy	ND
Sauret et al.	70/m	Biopsy	NP
Greb et al.	79/m	Biopsy	ND
Wakabayashi et al.	77/m	Halo sign	ND
Sardo et al.	78/m	Biopsy	FDG-PET/CT

**Note:** NP: Nothing Particular; ND: Not Done; US: Ultrasound; TA: Temporal Artery.

In three patients clinical features appeared after the first or second or third dose of Pfizer-BioNTech and one patient

represented clinical appearances following the second dose of mRNA vaccine. Two patients presented with clinical findings

after the first or second dose of COVID-19 vaccine (ChAdOx1) (Table 2). Regarding the adverse effect, the trends of molecular medicine suggested that the characteristic features of the spike protein itself either due to molecular mimicry with human tissues or as an ACE2 ligand may cause the mRNA vaccination mediated adverse effects such as an autoimmune disease [5]. The study indicated that the mRNA used in mRNA vaccine represents both antigen and adjuvant, leading to cause inflammation and immunity response [6]. In addition, it is known that IFN-1 induced by COVID-19 mRNA and adenovirus vector vaccines may also produce inflammatory and cytotoxic mediators, and

CD4<sup>+</sup> T follicular helper cells [4,6]. Chen et al. described that molecular mimicry, autoantibodies production, and the certain vaccine adjuvants contribute to induce the autoimmune phenomena following COVID-19 vaccination [1]. Recent reports suggested that the development of GCA after COVID-19 vaccination may be attributed to the cross-reactivity [49,57]. Based on the evidence, the development of GCA after COVID-19 vaccine may be attributed to the molecular mimicry along with IFN-1 immune response in old predisposed individuals.

**Table 2:** GCA following COVID-19 vaccine (COVID-19 vaccine status).

Study	Age/sex	COVID-19 vaccine	Time from vaccination
Anzola et al.	83/f	Pfizer/BioNTech	24 h after first dose
Gambichler et al.	82/m	Pfizer/BioNTech	10 days after second dose
Sauret et al.	70/m	AstraZeneca	A few days after first dose
Greb et al.	79/m	mRNA	2 days after second dose
Wakabayashi et al.	77/m	Pfizer/BioNTech	1 day after third dose
Sardo et al.	78/m	AstraZeneca	4 weeks after second dose

**Note:** Pfizer/BioNTech; BNT162b2, Moderna; mRNA-1273, AstraZeneca; AZD1222

Further researches and studies are needed to clarify the pathogenesis of the development of GCA after COVID-19 vaccination.

## CONCLUSION

The abnormal immune response derived from aged immune system and age-related changes in blood vessels such as senescent endothelial cell and vascular smooth muscle cell may contribute to induce the development of giant cell arteritis. The development of giant cell arteritis after COVID-19 vaccination may be attributing to the molecular mimicry along with the IFN-1 immune response in old predisposed individuals. Further investigation is needed to elucidate the pathogenesis of the development of giant cell arteritis after COVID-19 vaccination.

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