



Generalized Morphea after COVID-19 Vaccination along with Characteristic Nature of Spike Protein

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ABSTRACT

The previous reports suggested that Coronavirus Disease 2019 (COVID-19) may be a systemic endothelial disease or a multi-organ disease including endotheliitis, hypercoagulability, and cytokine storm especially in severe type. One of the most common skin presentations associated with COVID-19 is chilblain, involving the pathogenesis of vasospasm and the type 1 interferon (IFN-1) immune response. Recent report suggested that cleaved Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spike protein may exist in cutaneous endothelial cells and eccrine epithelium, showing a pathogenetic mechanism of COVID-19 endotheliitis. The mRNA COVID-19 vaccines contributed to the induced neutralizing humoral and cellular immunity, decreased infections, hospitalizations, and deaths. Meanwhile, molecular medicine indicated that the characteristic nature of the spike protein itself may cause vaccination-mediated adverse effects. In this article, current knowledge and trends of morphea after COVID-19 vaccine along with adverse effects due to the characteristic nature of spike protein have been reviewed. Recent study suggested that the prolonged presence of mRNA vaccine in lymph nodes and spike antigen in lymph nodes and blood, and the interactions between free-floating spike protein/subunits/peptide fragments and Angiotensin-Converting Enzyme 2 (ACE2) in the blood or lymph node, or ACE2 expressed in cells induced the molecular mimicry with human tissues or as an ACE2 ligand. It is supported that the IFN-1 induced by COVID-19 mRNA and adenoviral vector vaccines might contribute to induce morphea. Most patients showed the generalized morphea suggesting that the development of severe type may be attributed to the molecular mimicry along with IFN-1 immune response.

Keywords: COVID-19 vaccination; Generalized morphea; Spike protein; IFN-1; Molecular mimicry

INTRODUCTION

The previous reports have suggested that COVID-19 may be a systemic endothelial disease or a multi-organ disease including endotheliitis, hypercoagulability, and cytokine storm especially in severe stage [1]. Cappel et al. described that one of the most common skin presentations associated with COVID-19 is chilblain speculating the mechanism of interplay through ACE2, the Renin-Angiotensin-Aldosterone System (RAAS), sex hormones, and the IFN-1 immune response [2]. Recent report described that the cleaved SARS-CoV-2 spike protein may exist in cutaneous endothelial cells and eccrine epithelium, showing a pathogenetic mechanism of COVID-19 endotheliitis [3]. The efficacy and safety of mRNA COVID-19 vaccines have contributed to the induced neutralizing humoral and cellular immunity, decreased infections, hospitalizations, and deaths [4]. Meanwhile, it is known that the characteristic nature of the spike protein itself either due to

molecular mimicry with human tissues or as an ACE2 ligand may cause the vaccination-mediated adverse effects such as autoimmune disease [5]. It is known that the IFN-1 induced by COVID-19 mRNA and adenovirus vector vaccines may also produce inflammatory and cytotoxic mediators, and CD4⁺ T follicular helper cells [6]. Some studies of morphea after COVID-19 vaccination have been suggested [7-10]. In this article, current knowledge and trends of morphea following COVID-19 vaccination along with adverse effects due to characteristic appearances of spike protein have been reviewed in detail.

LITERATURE REVIEW

Endothelial dysfunction in COVID-19

The expression of ACE2 was recognized in the respiratory epithelium, vascular endothelium, and other cell types. It is also

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known that SARS-CoV-2 infection depends on ACE2 and Trans Membrane Protease Serine 2 (TMPRSS2) as host cell factors [11]. The position paper recommended that the endothelial biomarkers and function such as Flow-Mediated Vasodilation (FMD) should be assessed for their usefulness of the risk stratification in patients with COVID-19 [12]. The previous reports have suggested that COVID-19 may be a systemic endothelial disease or a multi-organ disease including endotheliitis, hypercoagulability, and cytokine storm especially in severe stage [1]. With respect to the SARS-CoV-2 Omicron variant, the importance of estimation of the endothelial function evaluated by FMD test has been indicated because this strain exhibited more efficient transduction of ACE2-expressing target cells, leading to endothelial dysfunction [13]. Regarding Multisystem Inflammatory Syndrome in Children (MIS-C) patients, the assessment of endothelial function for risk stratification, follow-up of convalescence, and prediction of autoimmune disease have been suggested [14]. It is known that following acute COVID-19 infection, a patient with physical and neuropsychiatric manifestations lasting longer than 12 weeks is considered as Long COVID [15]. The persistent microvascular dysfunction demonstrated by microvascular changes (capillary changes and nailfold videocapillaroscopy: NVC features) along with ET-1 level after COVID-19 infection has been previously suggested [16]. It has been proposed that Flow-Mediated Vasodilation (FMD) and Nitroglycerin-Mediated Vasodilation (NMD) in the brachial artery are potential procedures for assessing Vascular Endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis status [17-19]. Several reports in COVID-19 using FMD and endothelial biomarkers examinations have been provided [20-24].

Suggestive of COVID-19 with positive immunohistochemistry for SARS-CoV-2 spike protein in dermatology

Larenas-Linnemann et al. described skin manifestations related to COVID-19 immune dysregulation such as pseudo-chilblain and morbilliform/maculopapular in the pediatric cases suggesting that the plausible pathophysiological mechanisms may be vasculitis-like reactions, direct virus-induced cutaneous damage, and/or indirectly systemic inflammatory reaction [25]. Cappel et al. mentioned that the most common skin presentations associated with COVID-19 is chilblain, speculating that the mechanism for COVID-19-related chilblain has an interplay through ACE2, the RAAS, sex hormones, and the IFN-1 immune response [2]. Previous study suggested virus-induced vascular damage and ischemia as the pathophysiology of COVID-19-associated chilblains showing the evidence of cytoplasmic granular positivity for SARS-CoV-2 spike protein in endothelial cells by immunohistochemistry and the presence of viral particles using electron microscopy [26]. Meanwhile, previous report provided a feature of endotheliitis and similar to autoimmune vasculitis, along with negative for in situ test in patients with COVID-19 [27]. The study suggested that COVID-19 skin lesions are rarely positive at RT-PCR test and supported the theory that IFN-1 response and immune response rising the vascular damage serve as a crucial role in the development of the skin manifestations such as chilblain-like lesions [28]. Recent study provided that the cleaved SARS-CoV-2 spike protein may be present in cutaneous endothelial cells and eccrine epithelium, showing a pathogenetic mechanism of COVID-19 endotheliitis [3]. Regarding pityriasis rosea-like eruptions, the study also showed that immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein

was positive on the endothelium and perivascular lymphocytes, suggesting that this tool may show an important determination in the diagnosis of COVID-19 in negative serology or PCR patients [29].

Morphea (localized scleroderma)

Morphea (Localized scleroderma) showing a spectrum of sclerosis disease affects adjacent tissues such as the fat tissue, fascia, muscle, and bone without involving internal organs [30]. According to Laxer and Zulian, morphea is classified into 5 types including circumscribed, linear, generalized, pansclerotic, and mixed types [31]. Infections, trauma, radiation, and drugs as causative factors for morphea may induce microvascular injuries and activate T-cell status, subsequently leading to a release of adhesion molecules such as soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) and soluble Intercellular Adhesion Molecule-1 (sICAM-1). In result, pro-fibrotic mediators such as Transforming Growth Factor-Beta (TGF- β), platelet-derived growth factor, connective growth factor, IL-4, IL-6, IL-8, and chemokines are released as previously described [30]. It is also known that endothelial cell damage showed the initial step in the development of soft tissue alterations in patients with morphea, suggesting that virus infection may induce vascular damage through neo-intimal proliferation and apoptosis by the overproduction of profibrotic cytokines such as TGF- β [32]. However, it is known that the transition from morphea to Systemic Sclerosis (SSc) does not develop. Meanwhile, SSc is an autoimmune disease characterized by fibrosis such as skin and internal organs with vascular injury and immune system disorders [33]. The joint committee of the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) provided the 2013 new classification criteria for systemic sclerosis [34]. It is known that the most characteristic autoantibodies related to SSc are anti-centromere, anti-topoisomerase-I, and anti-RNA polymerase III. Recently, endothelial dysfunction using brachial Flow-Mediated Vasodilation (FMD) and carotid Intima-Media Thickness (IMT) as measures of cardiovascular risk have been investigated in patients with SSc [35].

Comparison between US and histopathological features in morphea

The Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) including the Localized Scleroderma Activity Index (LoSAI) and The Localized Scleroderma Damage Index (LoSDI) associated with Physician's Global Assessment (PGA) is clinically promising [36,37]. Additionally, PGA includes disease activity (PGA-A) and damage (PGA-D). In currently dermatologic field, several reports focusing on ultrasonographic (US) features of the dermal involvement such as morphea and intradermal nodular fasciitis have been reported [38,39]. In addition, the new procedure can contribute to the accurate ultrasonographic diagnosis for dermatological superficial lesion, especially dermal involvement, namely thickness, echogenicity, and vasculature condition without a copious amount of gel [40]. Due to the complex disease, the accurate diagnosis, assessment of disease severity and tissue damage in morphea have been required. According to previous report, the clinical and laboratory markers of this entity do not provide anatomical status of disease severity and activity [38]. Thickening and decreased echogenicity of the dermis and increased echogenicity of the subcutaneous tissue, along with increased dermal vascularity were depicted during the active phase on gray scale and color Doppler

US [41]. Histopathologically, the thickened collagen bundles within the reticular dermis including the dense inflammatory infiltrations between the collagen bundles and around blood vessels, and sweat glands are the characteristic features of morphea during the active stage [30, 42]. While substantial atrophy of the dermis and subcutaneous tissue during the late phase were observed on US. Histological aspects show collagen fibers, the relatively avascular status, along with the presence of the little inflammation during the late stage [30,42]. According to previous study, the Ultrasound Morphea Activity Score (US-MAS) was performed for estimating Methotrexate (MTX) based on ultrasound assessment of activity of morphea suggesting that the results is the low effectiveness of methotrexate in the patients with morphea [36,43].

Correlation between endothelial function and disease activity in morphea Adhesion molecules such as VCAM-1 and ICAM-1 are released by the induced microvascular injuries and activated T-cell status in morphea as previously described [30]. Yamane et al. indicated the increased the sVCAM-1 and E-selectin in patients with localized scleroderma, suggesting that these findings may reflect the disease severity and contribute to monitor the endothelial activation status [44]. The endothelial dysfunction in patients with localized scleroderma is associated with different phenotype of the disease course as previously described [45]. Meanwhile, the study provided that endothelin-1, sE-selectin and hsCRP levels were significantly higher in patients with Raynaud's phenomenon showing that microvascular endothelial dysfunction may be associated with Raynaud's phenomenon [46].

Morphea after COVID-19 infection

Regarding immunological dysfunction, previous study demonstrated that combinations of the inflammatory mediators including IFN- β , PTX3, IFN- γ , IFN- λ 2/3, and IL-6 have been associated with Long COVID [47]. Results provided a persistent inflammatory response following mild-to-moderate acute COVID-19 infection suggesting the possibilities including sustained antigen, autoimmunity driven by antigenic cross-reactivity or a reflection of damage repair [47].

It has been suggested that the effect on COVID-19 for autoimmune skin diseases can induce exacerbation of a pre-existing disease, change of disease presentation, and developing the disease [48,49]. It has been reported that the development and worsening of inflammatory skin diseases following COVID-19 infection induced by abnormal activation of the immune system [50]. Previous report showed morphea induced by SARS-CoV-2 infection based on the histological features suggesting that a molecular mimicry has been supposed. Another study showed a case of pansclerotic morphea following COVID-19 infection based on the clinical and pathological features, suggesting the presence of new cutaneous diseases after COVID-19 infection [48].

Adverse effects following COVID-19 mRNA vaccination

Three vaccines including the BNT162b2 mRNA, the mRNA-1273, and Ad26.COV2.S of which use the original wild-type SARS-CoV-2 spike protein first identified in Wuhan, China in 2019 have been provided [4]. In dermatology, previous study indicated that plausible pathomechanisms of COVID-19 vaccine-induced cutaneous reactions including type I hypersensitivity, type IV hypersensitivity, molecular mimicry, and autoimmune mechanisms [51]. Though anti-SARS-CoV-2 mRNA vaccines such as the BNT162b2 and mRNA-1273 vaccines mobilize innate, humoral,

and cellular adaptive immune responses, the rare manifestations as adverse effects including Guillain-Barre syndrome, myocarditis/pericarditis, lymphadenopathy, herpes zoster reactivation, and autoimmunity have been reported [5]. Meanwhile, it is suggested that the immune response towards autoimmune-like tissue damage induced the immune-mediated hepatitis [52]. 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 [53]. They suggested that mRNA vaccinations stimulate GCs containing vaccine mRNA and spike antigen up to 2 months after vaccination, showing a prolonged presence of vaccine mRNA in Lymph Nodes (LNs) GCs and spike antigen in LN GCs and blood [53]. Trougakos et al. suggested that the research of mechanistic details of sustained spike mRNA and protein production for a prolonged presence in human tissues is important [54]. Trougakos et al. described the adverse effects after vaccination which may associate with a proinflammatory behavior of the lipid nanoparticles used [5]. They also suggested that adverse effects mediated by vaccination can be attributed to the characteristic nature of the spike protein either due to molecular mimicry with human proteins or as an ACE2 ligand. It is indicated that the vasculature is sensitive to free-floating spike fragments, and these effects along with the systemic immune response to the spike antigen can lead to persistent inflammation in multiple vascular beds [5,55]. The report also showed that spike protein increased IL-6/IL-6R-induced trans signaling response and alarmin secretion in human endothelial cell [5]. As spike protein production induced by vaccine occurs in internal organs and tissues leading to exert systemic effects, the recent report recommended the identification of the individuals with risk for adverse reactions [56].

Morphea following COVID-19 vaccination

The mRNA-1273 vaccine is a lipid nanoparticle-encapsulated mRNA-based vaccine manufactured by Moderna and the BNT162b2 mRNA is a lipid nanoparticle-formulated nucleoside-modified RNA vaccine manufactured by Pfizer-BioNTech [57,58]. Meanwhile, the Ad26.COV2.S is a human adenovirus type 26 vectored vaccine manufactured by Jansen/Johnson & Johnson [59]. The COVID-19 vaccines contributed to the induced neutralizing humoral and cellular immunity, decreased infections, and deaths. Meanwhile, previous study described the plausible pathomechanisms of COVID-19 vaccine-induced cutaneous lesions including type I hypersensitivity, type IV hypersensitivity, molecular mimicry, and autoimmune mechanisms, emphasizing that the molecular mimicry between SARS-CoV-2 spike-protein and human tissues may induce autoimmune-mediated reactions [51]. 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].

DISCUSSION

The study provided that the prolonged presence of mRNA vaccine and spike antigen, and the plausible interactions between free-floating spike protein/subunits/peptide fragments and ACE2 may lead to the molecular mimicry with human tissues or as an ACE2 ligand [5]. It is known that IFN-1 induced by COVID-19 mRNA and adenovirus vector vaccines may also produce inflammatory

and cytotoxic mediators, and CD4⁺ T follicular helper cells [6]. In this article, current knowledge and trends of morphea following COVID-19 vaccination along with adverse effects due to characteristic appearances of spike protein have been reviewed. Metin et al. reported a case of morphea after the COVID-19 mRNA vaccine [7]. They concluded that positive expression using anti-spike glycoprotein 1 monoclonal antibody may have been the result of cross-reactivity, suggesting that expressed proteins may be tissue components [7]. Previous study showed four cases of generalized morphea following COVID-19 vaccine, indicating that the molecular similarity between COVID-19 vaccine and human proteins and the effects of autoreactive lymphocytes may induce autoimmune disease [8,51]. They also described that COVID-19 mRNA and recombinant adenoviral vector vaccines may contribute to drive the activation of chemokines, cytokines, suggesting that especially, activation of IFN-1 may serve as a crucial role in the development of morphea and systemic sclerosis [8]. Recent study also provided the two cases of the generalized morphea after the COVID-19 vaccination, suggesting that the features of cutaneous

reactions after COVID-19 vaccination may be attributed to the molecular mimicry [9]. It is also plausible that mRNA-based vaccines exhibited the production of antibodies and the cellular responses toward CD4⁺ and Th1 cells [9,60]. Oh et al. have also reported a case of generalized morphea after Pfizer-BioNTech vaccine [10]. The studies of morphea after COVID-19 vaccination are bibliographically shown in Tables 1 and 2 [7-10]. In six patients skin lesions appeared after the first and/or second dose of Pfizer-BioNTech vaccine whereas one patient represented cutaneous lesions following the first dose of mRNA-1273 COVID-19 vaccine. One patient showed skin lesions 20 days after the second dose of AstraZeneca COVID-19 vaccine (Table 2). Seven of the 8 patients developed morphea after mRNA vaccination. Of eight patients in the four studies, seven patients showed generalized morphea as a severe type after COVID-19 vaccination, suggesting that this result may be attributed to the molecular mimicry along with IFN-1 immune response [8-10]. Further study is needed to elucidate the pathogenesis of the development of morphea after COVID-19 vaccination.

Table 1: Morphea after COVID-19 vaccine (clinical features).

Study	Age/sex	Past history	Lesion locations
Metin, et al. [7]	55/f	NP	Breast
	61/f	NP	Abdomen, back, limbs
Paolino, et al. [8]	52/f	EF	Abdomen, chest, limbs
	64/m	NP	Abdomen, limbs
	73/f	AV block	Abdomen, limbs
Antonanzas, et al. [9]	45/f	NP	Back, thigh
	52/f	NP	Abdomen, thigh
Oh, et al. [10]	47/f	NP	Thigh, arm, calf

Note: NP: Nothing Particular, EF: Eosinophilic Fasciitis, AV block: Atrioventricular block.

Table 2: Morphea after COVID-19 vaccine (COVID-19 vaccine status).

Study	Age/sex	COVID-19 vaccine	Time from vaccination
Metin, et al. [7]	55/f	Pfizer/BioNTech	4 weeks after 2nd dose
	61/f	Pfizer/BioNTech	15 days after 1st and 2nd dose
Paolino, et al. [8]	52/f	Pfizer/BioNTech	7 days after 2nd dose
	64/m	AstraZeneca	20 days after 2nd dose
	73/f	Pfizer/BioNTech	20 days after 2nd dose
Antonanzas, et al. [9]	45/f	Moderna	2 weeks after 1st dose
	52/f	Pfizer/BioNTech	6 weeks after 2nd dose
Oh, et al. [10]	47/f	Pfizer/BioNTech	3 weeks after 2nd dose

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

CONCLUSION

The prolonged presence of mRNA vaccine and spike antigen, and the plausible interactions between free-floating spike fragments and ACE2 may lead to the molecular mimicry with human tissues or as an ACE2 ligand. Additionally, type 1 interferon induced by COVID-19 vaccine may also contribute to induce morphea. Though further study is needed to elucidate the pathogenesis of the development of morphea after COVID-19 vaccination, the most patients in four studies showed generalized morphea as a severe type after COVID-19 vaccination, suggesting that this result may be attributed to the molecular mimicry along with type 1 interferon immune response.

CONFLICTS OF INTEREST

I declare that I have no conflict of interest.

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