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Comprehensive Assessment of the Impact of COVID-19 on Scleroderma and Morphea: Unraveling Interactions, Clinical Manifestations, and Therapeutic Implications

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Abstract

This review thoroughly examines the intricate pathophysiological dynamics and consequential clinical implications associated with heightened inflammatory dermatological responses in the context of COVID-19 vaccinations and acute or chronic COVID-19 infections, including post-COVID syndrome. Through a meticulous synthesis of existing scientific literature and recent research findings, our objective is to comprehensively examine the nuanced pathology and physiology underlying the exacerbation of scleroderma and morphea induced by SARS-CoV-2 infection and vaccination. The discussion encompasses considerations of cytokine dysregulation, immune cell activation, and their respective contributions to the increased susceptibility of the skin during COVID-19. Furthermore, a discerning analysis of scleroderma and morphea offers valuable perspectives on diagnostic nuances, prognostic intricacies, and potential therapeutic modalities. In addition to consolidating existing knowledge, this investigation underscores critical areas for future research, shedding light on the gaps inherent in the current literature. This review not only advances our contemporary understanding of the virus's inflammatory dermatological implications on scleroderma and morphea but also emphasizes the urgency for ongoing scholarly exploration to address nuanced gaps and intricacies inherent in this complex interplay, considering a spectrum of inflammatory skin conditions affected by COVID-19.

Introduction

The pandemic of COVID-19 brought about changes in our healthcare system and new manifestations of previously identified disorders and diseases. The World Health Organization (WHO) declared COVID-19 a worldwide pandemic in March 2020 and cautioned those with respiratory illness symptoms to quarantine themselves, which quickly transitioned into a global shutdown [1]. Primary symptoms of COVID-19 infection include fever, cough, dyspnea, malaise, fatigue and respiratory tract secretions. In a 2021 study, it was found that 20.45% of the reported literature on COVID-19 indicated the presence of dermatologic manifestations in the disease presentation [2]. The true pervasiveness of skin-related symptoms during the early stages of the pandemic may have been skewed due to limitations in conducting comprehensive patient examinations, obtaining proper pathology, and proper photographic documentation, due to restricted access and a shortage of healthcare personnel [3]. Skin involvement in COVID-19 encompasses a spectrum, spanning from infection-mediated manifestations to maculopapular rashes, chilblains (often referred to as "COVID toes"), and vesicular and livedoid patterns, all of which are related to the underlying mechanisms of COVID-19 infection [3].

Our review focuses on both new-onset and exacerbation of scleroderma and morphea in patients who have contracted COVID-19 or have received COVID-19 vaccinations. Scleroderma, or systemic sclerosis, is an autoimmune disorder that affects connective tissue mainly involving the skin but can invade the bones, muscles, and internal organs. This causes thickening and hardening of the body's tissues, which can mount an immune response that damages blood

vessels and tissues, leading to scar formation with an excess of collagen [4]. Morphea is a form of localized scleroderma that involves the skin and potentially the subcutaneous tissues. Although localized, morphea can result in debilitating lesions such as joint contractures or limb growth defects in children [5]. Due to their status as chronic diseases with potential multiorgan involvement and treatments commonly involving immunosuppressants, both scleroderma and morphea exhibited a notable prevalence in occurrence and recurrence during COVID-19 [6]. Scleroderma and COVID-19 also share disease features including pulmonary involvement and microangiopathy due to the overlapping mechanisms like molecular mimicry, cytokine storms, and endothelial injury, leading to heightened disease severity.

This study is aimed at elucidating the intricate pathophysiology of COVID-19 and vascular changes with resultant immune response that lead to inflammatory skin responses. We delineate the disease overlap and provide insight on prognosis, diagnosis, and treatment through a systematic review of the current literature on scleroderma and morphea in the context of COVID-19 infection and vaccination.

Methods

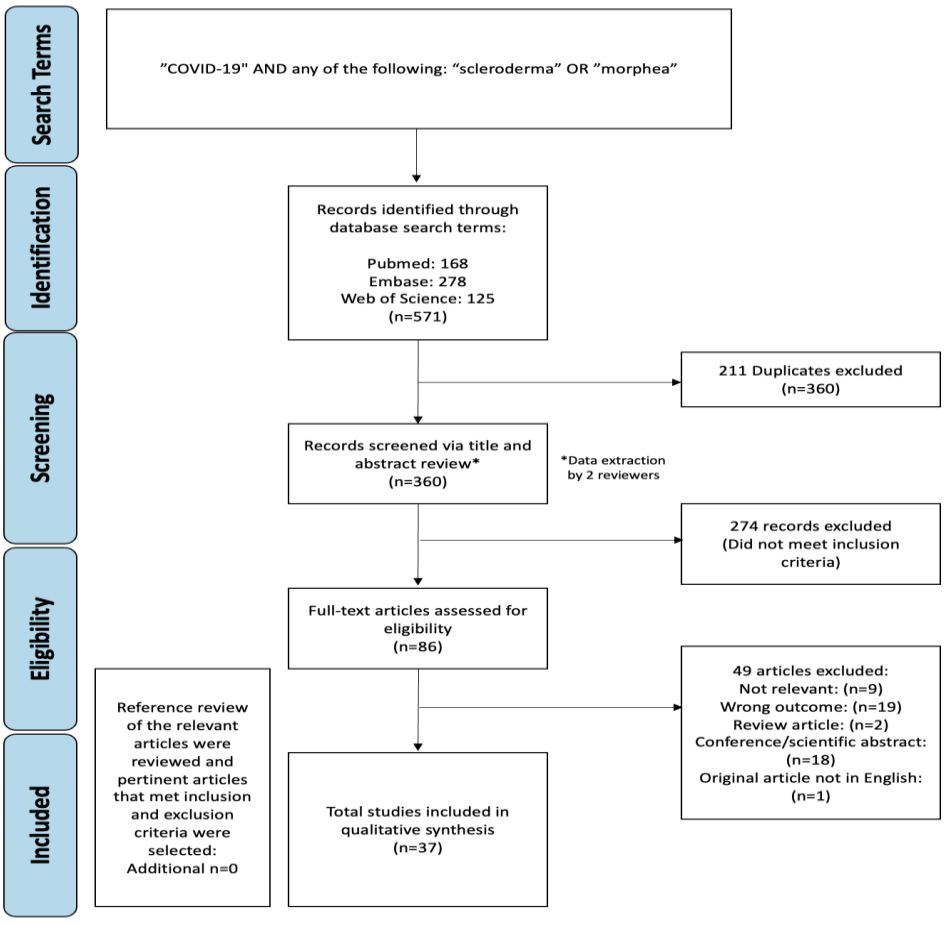
A systematic review of the published literature was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The literature search was performed on January 3, 2024, and included PubMed, Embase, and Web of Science databases. Search terms used were “COVID-19” AND any of the following: “scleroderma” OR “morphea”. Studies were included if they were published in the English language and reported patient data on the new-onset or exacerbation of scleroderma or morphea symptoms after COVID-19 infection or vaccination. Exclusion criteria consisted of review articles, scientific posters and abstracts, studies involving non-human subjects, and patient population less than 18 years.

All titles and abstracts were screened for relevance and duplicates between databases were removed. Full-text articles for the remaining studies were reviewed independently by two investigators (VL and MS). The reference lists of the full-text articles were analyzed for any additional relevant studies. All studies that met the specified criteria were included in the analysis.

Results

The initial search identified 571 articles; 211 duplicates were removed; 360 studies were screened by title and abstract; 274 studies were eliminated based on inclusion and exclusion criteria; 86 articles underwent full-text review. A total of 37 articles were included in the analysis. Figure 1 illustrates the breakdown of the literature search.

Figure 1. Diagrammatic representation of the literature search.



Our analysis included 37 studies involving four categories of scleroderma and morphea: new-onset scleroderma, scleroderma exacerbation, new-onset morphea, and morphea exacerbation. The results of the included studies are summarized in Tables 1-4.
Scleroderma results table

New-onset scleroderma

Eight studies in our analysis identified nine patients with new-onset scleroderma triggered by COVID-19 infection or vaccination, ranging between their 40s and 77, with the majority being female (66.7%, n=6) [7-14]. 55.6% (n=5) were linked to COVID-19 infection [7,8,11,12,13], while 44.4% (n=4) followed COVID-19 vaccination [9,10,14]. The time from exposure to onset varied broadly, spanning from 4 to 90 days. The shortest onset time was reported in a 74-year-old female post-vaccination, who was simultaneously diagnosed with chronic myelomonocytic leukemia with limited cutaneous systemic sclerosis [14]. The longest onset time was reported for a 67-year-old female with a prior Sjogren's syndrome diagnosis who presented with Raynaud phenomenon, fibrosis of the face and hands, and hypertension, which rapidly progressed to scleroderma renal crisis (SRC) [13].

Skin manifestations varied among patients and ranged from heliotrope rash to ulceration, with Raynaud phenomenon and skin fibrosis being most commonly reported. Systemically, the condition manifested in diverse ways including increased levels of creatinine kinase (CK), anemia, thrombocytopenia, interstitial lung disease (ILD), cardiac changes, and in some severe cases, hypertensive crisis with renal failure. Interestingly, antibody profiles were not uniform across patients; many tested positive for antinuclear antibody (ANA) among others such as anti-nuclear ribonucleoprotein (RNP), anti-Sjogren's syndrome A (SSA), anti-Scl-70, and more.

Therapeutic approaches adopted for these patients were as diverse as their symptoms. Treatments included calcium channel blockers, prednisone, mycophenolate mofetil (MMF), and nifedipine. Patient responses to these treatments were equally varied, with many showing improvement, some continuing to progress, and a few unfortunately succumbing to the condition or its complications.

Scleroderma exacerbation

Our analysis included eleven studies highlighting the exacerbation of scleroderma post-COVID-19 infection or vaccination [15-25]. Among the eighty-two patients studied, the age distribution spanned from 32 to 94 years. While the gender of many patients wasn't specified, of the nine reported cases, six (66.7%) were identified as female. A majority, 92.7% (n=76), experienced exacerbations following vaccination [16,20,21,23,25], while a smaller proportion, 7.3% (n=6), exhibited symptoms post-infection [15,17-19,22,24]. The interval between COVID-19 exposure and symptom onset varied, with recorded cases ranging from 1 week to 10 months. The most rapid onset manifested in a 34-year-old female post-vaccination, who developed a severe scleroderma flare characterized by facial and hand skin fibrosis, sclerodactyly, oral telangiectasias, and hypertension, resulting in a scleroderma renal crisis diagnosis [20]. The longest onset time occurred in a 94-year-old male post-vaccination, with a history of scleroderma renal crisis a decade earlier and systemic sclerosis in remission, presenting without skin symptoms but with significant extremity edema and renal complications [23].

Skin manifestations were a common finding among the cases, with patients experiencing a spectrum of conditions from widespread skin thickening and contractures to chilblain-like lesions, Raynaud phenomenon, and ulcers. Systemic manifestations were equally diverse and severe, with patients showing increased lactate dehydrogenase (LDH) levels, hypertension, ischemic glomerular changes, and structural heart alterations among others. Interestingly, a larger study within our review, involving 932 patients, reported worsening of at least one symptom of scleroderma in 6-8% of patients after vaccination; this included Raynaud's phenomenon, fatigue, muscle weakness, and gastrointestinal issues.

Treatment regimens varied greatly, including the use of methylprednisolone, low molecular weight heparin (LMWH), glucocorticoids, ACE inhibitors, MMF, and others. Outcomes also varied, with many patients showing improvement, some resolving entirely, while others did not report outcomes.

New-onset morphea

The analysis of fifteen studies revealed that new-onset morphea due to COVID-19 was documented in a total of 20 patient cases, with 90% (n=18) of these cases being female patients [26-40]. Among these patients, five (25%) developed new-onset morphea after contracting the COVID-19 infection [26,27,29,30,40]. Fifteen (75%) patients experienced new-onset morphea following COVID-19 vaccination [28,30-39]. The age range amongst all patients who developed new-onset morphea ranged from 29 to 79 years. The onset of morphea after exposure to the COVID-19 infection or vaccination ranged from 2 days to 5 months, with two cases lacking specific timing information [26,31].

Skin manifestations varied amongst the patients and included sclerotic lesions spreading across the abdomen and extremities, sclerosis of pretibial regions, and the presence of brown and violaceous plaques with sclerotic appearance. Treatment strategies for these patients varied and included topical clobetasol propionate, topical calcipotriol, vitamin E emollient, mycophenolic acid, phototherapy, methotrexate, tacrolimus cream, topical betamethasone, mometasone ointment, and tocilizumab. Some patients had unreported outcomes, but among those with reported outcomes, improvement or resolution was observed in their condition.

Morphea exacerbation

Three studies in our analysis discussed morphea exacerbations attributed to COVID-19 [41-43]. One case of morphea exacerbation occurred two weeks after the COVID-19 vaccination [41]. This patient was a 68-year-old female with a ten-year history of plaque morphea, which had been

in remission. She presented with brownish-purplish plaques with mild erythematous borders and sclerosis in areas of previous morphea lesions, without any systemic manifestations. Treatment with 15 milligrams (mg) of methotrexate weekly alongside folic acid led to improvement within three weeks. Another case involved morphea exacerbation three days after receiving the COVID-19 vaccination [43]. This patient was a 68-year-old female with a history of localized scleroderma and pre-existing morphea lesions. The patient was prescribed clobetasol propionate and desloratadine 5 mg once daily, resulting in the resolution of symptoms within seven days. The third case involved morphea exacerbation following COVID-19 infection, which occurred eight weeks prior, in a 45-year-old female with a history of morphea [42]. She presented with several brown and violaceous plaques featuring firm ivory centers coalescing with islands of sparing normal skin on the trunk and leg. No systemic manifestations were observed in this case. The patient was treated with narrow-band ultraviolet (UV)B phototherapy but did not return for follow-up.

Discussion

Overview

This comprehensive review explores the complex pathophysiological dynamics underlying inflammatory dermatological responses, focusing on scleroderma and morphea, in both acute and chronic phases of COVID-19 infections and in response to vaccinations. Drawing from the analysis of 37 pertinent studies, the findings shed light on distinct outcomes such as new-onset and exacerbations of scleroderma and morphea post-COVID-19 infection or vaccination. Importantly, while dermatological changes manifested in different forms, including heliotrope rash and sclerosis, systemic complications were evident through the elevation of a variety of biomarkers, such as creatinine kinase and lactate dehydrogenase. This underscores the need for comprehensive and multifaceted treatment strategies. Furthermore, this review highlights the shared pathophysiologic mechanisms between COVID-19 and scleroderma/morphea, including endothelial damage, molecular mimicry, and cytokine storms, emphasizing the need for distinct diagnostic, prognostic, and therapeutic strategies navigating this intricate relationship.

Pathophysiological dynamics

COVID-19 and vascular changes

The intricate relationship between COVID-19 and endothelial cells suggests that COVID-19 can be viewed as a vascular disease, much like scleroderma. The normal vascular endothelium is responsible for preventing thrombosis by regulating interactions between platelets and endothelial cells. Additionally, it generates nitric oxide (NO), crucial for vascular tone and protecting the endothelium from oxidative injury [44]. Autoptic studies revealed that SARS-CoV-2 infection induces a wide range of effects on the endothelium, leading to severe endothelial injury, capillary inflammation, and widespread thrombosis with microangiopathy [45]. This endothelial dysfunction results in a procoagulant state, vasospasm, and inflammation, disrupting normal vascular function. Similarly, scleroderma is characterized by endothelial dysfunction, which reduces NO production, increases adhesion molecule expression, and promotes platelet aggregation and vascular wall thickening [45]. These vascular changes contribute to the complications and thrombotic events associated with the disease.

While both COVID-19 and scleroderma exhibit increased vascular permeability, coagulation, and microthrombosis, they also present with other distinct vascular changes. Scleroderma primarily manifests vascular fibrotic changes, the initial trigger of which remains unclear. In contrast, COVID-19 infections often show macrothrombosis, with the virus directly invading endothelial cells and triggering neutrophil extracellular traps (NETs) [45]. As a result, COVID-19 induces vascular changes via endothelial cell dysfunction, leading to thrombosis, inflammation, and vasospasm. Such vascular alterations can exacerbate scleroderma, amplifying its vascular manifestations and complications.

Immune response alteration

Recent studies have confirmed that viral illnesses can trigger autoimmune disorders like scleroderma and morphea [7,46]. The immune response elicited by COVID-19 has the potential to exacerbate or modify the immune-mediated pathophysiology of scleroderma and morphea via mechanisms involving cytokines, antibody production, molecular mimicry, and immune cell activation. The relationship between COVID-19 and autoimmune conditions like scleroderma centers around dysregulated cytokine responses and immune-mediated pathophysiology. The COVID-19 infection is characterized by the release of proinflammatory cytokines and chemokines, like interleukins (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF-a). These mechanisms, in turn, contribute to furthered fibroblast activation and increased collagen production, exacerbating skin fibrosis in patients with scleroderma. Additionally, the cytokine milieu associated with COVID-19 infection likely amplifies the existing cytokine dysregulation seen in scleroderma.

Moreover, the immune response to COVID-19 infection involves the production of antibodies against SARS-CoV-2. In individuals with scleroderma or morphea, this heightened antibody production may inadvertently stimulate B cells to produce autoantibodies or bolster existing ones, perpetuating autoimmune reactions and tissue damage. Furthermore, it has been found that COVID-19 can trigger autoimmunity through molecular mimicry [7]. Molecular mimicry occurs when a foreign antigen closely resembles host proteins, causing the immune system to less effectively distinguish between the two, disrupting self-tolerance. The immune response initiated against the foreign antigen may inadvertently target the host's tissues, activating autoreactive T cells and promoting autoantibody development [46,47].

In scleroderma and morphea, the aberrant activation of immune cells plays a significant role in the development of tissue fibrosis, vascular abnormalities as previously mentioned, and inflammatory responses. In COVID-19, the

recruitment of macrophages, T cells, and B cells is a crucial part of the immune response against viral infection. This heightened immune activation may potentially synergize with the pathological immune cell responses observed in scleroderma, resulting in increased tissue damage and disease progression.

Additionally, as previously described, both COVID-19 and scleroderma are associated with endothelial dysfunction and vascular abnormalities. Therefore, endothelial injury induced by COVID-19 may exacerbate vascular complications in scleroderma and morphea. Overall, the synergistic effects of cytokine dysregulation, enhanced antibody production, and endothelial dysfunction in COVID-19 infections can aggravate the immune mediated pathophysiology of scleroderma and morphea.

Inflammatory dermatological responses

Cytokine storm and skin

Severe cases of COVID-19 can trigger a cytokine storm, characterized by the overproduction of inflammatory markers, notably IL-1, IL-6, IL-17 and TNF-a [48]. This hyperactivation of the immune response contributes to systemic inflammation, exacerbates localized inflammation in the skin in conditions like scleroderma, and may result in multi-organ failure and death. The elevated levels of proinflammatory cytokines stimulate fibroblast activation and collagen production, leading to increased skin fibrosis [49]. In scleroderma and morphea, this cytokine-driven fibroblast activation amplifies the pathological fibrotic processes, resulting in skin thickening, hardening, and scarring. To compound this, the excessive release of cytokines disrupts normal tissue repair mechanisms, impairing the resolution of inflammation and fibrosis in scleroderma. This creates a cycle of inflammation, fibrosis, and tissue damage, which is responsible for the chronic and progressive skin changes characteristic of these autoimmune conditions [50].

Cutaneous manifestations

The cutaneous manifestations of COVID-19 are numerous and vary widely among those affected. Following infection, the predominant cutaneous patterns can be described as maculopapular, urticarial, vesicular, chilblain-like, petechiae, and livedoid, with pseudo-chilblains most commonly reported among them [51,52]. In individuals with scleroderma or morphea who contract COVID-19, specific cutaneous manifestations may include exacerbation of fibrotic skin changes, increased vascular abnormalities, and altered presentation of skin lesions. The dermatological manifestations of scleroderma encompasses Raynaud's phenomenon, digital swelling, chilblains, telangiectasia, calcinosis, abnormal nail fold capillaries, and sclerodactyly [53]. The coexistence of COVID-19 with scleroderma or morphea can modify or exacerbate these cutaneous manifestations.

Based on the findings of this systematic review, it is evident that COVID-19 can have a significant impact on autoimmune diseases such as scleroderma and morphea. It has the potential to exacerbate pre-existing skin conditions, alter their presentation, or even potentially trigger these diseases for the first time [26]. These cutaneous changes arise through previously described mechanisms involving endothelial dysfunction, cytokine dysregulation, immune cell activation, and the transformation of endothelial cells into myofibroblasts.The intersection of COVID-19 with autoimmune diseases manifests through specific cutaneous changes and triggering mechanisms, highlighting the importance of carefully assessing skin changes in COVID-19 patients with pre-existing autoimmune conditions.

Diagnostic and prognostic considerations

Clinical features overlap

The clinical presentation, immune response, and underlying mechanisms of the COVID-19 virus often bear striking similarities to autoimmune disease, such as scleroderma; this similarity poses a challenge in distinguishing which features can be attributed to COVID-19 as opposed to an autoimmune condition [7,46]. Interestingly, both scleroderma and COVID-19 share systemic manifestations and display elevated levels of IL-6, IL-10, and monocyte chemoattractant protein (MCP)-1 [54,55]. Moreover, both conditions can result in endothelial damage and interstitial lung fibrosis [7].

Despite COVID-19 following an acute progression and scleroderma having a chronic nature, they share remarkable similarities in early disease states, such as vascular endothelial damage, thrombosis, and apoptosis. While both conditions exhibit significant lung inflammation and fibrosis, it is important to note that their underlying mechanisms differ [45]. In scleroderma, there is pulmonary lymphocyte infiltration and neutrophil extravasation into air spaces leading to damaged endothelial cells and narrowed blood vessels. Moreover, endothelial to mesenchymal transition (EMT) facilitates the transition to myofibroblasts, accelerating lung fibrosis. In contrast, COVID-19 is characterized by extensive neutrophil infiltration in the pulmonary capillaries, leading to inflammation and capillary leakage. While both diseases result in lung fibrosis, their mechanistic pathways diverge. Furthermore, disease specific autoantibodies, such as anti-Scl-70 and anti-centromere antibody (ACA), serve as critical biomarkers that distinguish scleroderma from other pathologies, including COVID-19.

Prognostic indicators

There are a multitude of prognostic indicators that can predict the course of scleroderma and morphea, particularly in the context of COVID-19. The variability in disease severity observed in scleroderma and morphea, especially their potential involvement with internal organs such as the lungs, holds clinical significance. Scleroderma and morphea, both chronic conditions, can impact clinical outcomes when these patients are acutely diagnosed with COVID-19. One example documented in the literature is the difficulty of distinguishing scleroderma-associated interstitial lung disease (SSc-ILD) and COVID-19. SSc-ILD is the scarring and inflammation of the alveoli in the lungs, which leads to difficulty breathing. The resemblance between SSc-ILD and COVID-19 presents a challenge for clinicians in

distinguishing whether a patient is concurrently experiencing a combination of both conditions or solely dealing with SSc-ILD, especially given their similar clinical presentation. The literature also highlights that interstitial lung disease (ILD) can potentially predispose individuals to a more severe form of COVID-19 infection, as the SARS-CoV-2 virus tends to reside in the lower respiratory tract, which may be compromised from damage caused by ILD [56].

Other notable prognostic factors include patient age, presence of comorbidities, and vaccination status. Advanced age, along with the presence of comorbidities, can increase the risk of severe outcomes in COVID-19 infections. This highlights the value of comprehensive care that addresses both scleroderma and morphea in conjunction with other comorbidities and aims to minimize complications arising from potential overlap or correlations between conditions. Furthermore, promoting preventive healthcare among females is of utmost importance, given that 80% of scleroderma cases occur in females, particularly within the age range of 30-50 years [57].

Impact on treatment regimens

It is crucial to consider the clinical implications of immunosuppressive medications in the context of COVID-19 and their potential to directly or indirectly alter typical treatment regimens for patients with scleroderma and morphea. Direct impacts include concerns about drug interactions. Due to the autoimmune nature of scleroderma and morphea, many patients receive immunosuppressive medications to manage the severity of their conditions. These medications can lower the body's ability to fight infections, making patients more susceptible to COVID-19 infection and its associated complications. To address these concerns, the International Societies of Rheumatology published practical recommendations aimed at mitigating the risk of COVID-19 infection in communities with rheumatic conditions and patients on immunosuppressive medications [58].

Indirect impacts involve the rise of telehealth services during the COVID-19 pandemic, which healthcare systems adopted to minimize the risk of SARS-CoV-2 transmission. While telehealth offers myriad benefits for patients across various medical specialties, it has limitations in dermatology, especially in the evaluation of skin conditions through smartphone or laptop screens compared to in-person examinations. This shift in healthcare delivery has affected how patients with scleroderma and morphea receive care [59].

From a preventive standpoint, the recommendations propose rapid laboratory and radiological screening if ILD is diagnosed secondary to SSc; this is to distinguish between an ILD flare and a potential SARS-CoV-2 superinfection. In terms of therapeutic modalities, the society suggests temporarily pausing immunosuppression during the course of COVID-19 infection to reduce immunosuppression when COVID-19 infection is suspected [58].

Despite its wide array of benefits in diverse clinical settings, telemedicine is currently limited in accurately diagnosing patients with rheumatic diseases, such as scleroderma, myositis, and vasculitis, as noted in the literature. These diagnostic limitations highlight the need for further investigation in this area. Logistically, the treatment landscape for scleroderma and morphea has been significantly influenced by various factors related to COVID-19. These challenges encompass delays and modifications in treatment plans due to disruptions in healthcare services during and after the pandemic, adjustments to medication regimens prompted by fluctuating resource availability, and the postponement of non-urgent and elective treatments and procedures [59].

Potential therapies

The current treatment options for morphea are quite limited, primarily relying on a combination of systemic corticosteroids and methotrexate. While these treatments can provide relief, they are not disease-specific and are associated with a range of long-term side effects, making them less than ideal [60]. However, there is a growing focus on new and innovative therapeutic strategies for managing both morphea and scleroderma. These approaches encompass a spectrum of possibilities, including antifibrotic agents, anti-inflammatory drugs, anti-senolytic therapies, cellular therapies, and gene-therapy interventions. These emerging strategies aim to provide more targeted and effective treatments, potentially reducing the reliance on non-specific medications with adverse side effects [60].

Phototherapy has emerged as another standard treatment for morphea, showing promise in addressing fibrosis and inflammation. Current clinical trials are investigating the nuances of phototherapy, with a particular emphasis on comparing different techniques such as UVA-1, UVB, and fractional carbon dioxide lasers. These studies aim to elucidate the most effective phototherapy approaches for targeting inflammation and fibrotic activity in morphea and related conditions, offering hope for improved treatment outcomes [61]. These advancements in therapeutic strategies hold the potential to significantly enhance the quality of care and outcomes for individuals with morphea.

Gaps in current research and future directions

Combination therapies have emerged as a promising approach for the treatment of inflammatory skin conditions. These therapies involve a range of strategies, including the use of anti-fibrotic and anti-inflammatory therapeutics, cell and gene therapies, and anti-senolytic approaches. Each combination aims to achieve specific treatment goals tailored to the condition and patient. A recent review published in *Nature* underscores the importance of this concept, emphasizing that effectively managing these conditions requires a deeper understanding of emerging medical imaging technologies and early intervention techniques [62].

Comparison with other conditions

The COVID-19 virus has been associated with various inflammatory skin conditions, including urticarial lesions, vesicular eruptions, pseudo-chilblains, and maculopapular rashes, as evidenced by histopathology reports describing lymphocyte infiltration with and without vasculitis [63]. The

mechanisms by which scleroderma and morphea occur in relation to COVID-19 infection and the COVID-19 vaccine are still under exploration. The lack of comprehensive understanding of this relationship has contributed to the diverse range of treatment options currently employed for scleroderma and morphea attributable to the virus, as previously mentioned. Similarly, the treatment approaches for other common inflammatory skin manifestations associated with COVID-19 are also subject to variation as ongoing research continues to uncover the mechanisms behind these conditions and their connection to the virus.

In cases of cutaneous vasculitis attributed to COVID-19, positive outcomes have been documented with the use of prednisolone in several cases. Current studies show that cutaneous vasculitis may occur due to the virus invading vascular endothelial cells in multiple systems throughout the body [64]. Moreover, it has recently been shown that COVID-19 can directly induce vasculitis through a specific immune response. As the mechanisms underlying these inflammatory skin conditions and their relation to COVID-19 continue to be explored, treatment modalities and the efficacy of therapies offered are expected to expand, potentially offering more targeted and effective approaches to managing these dermatological manifestations.

Wider clinical implications

The findings of this study support areas in which the management of scleroderma and morphea related to COVID-19 could have greater implications for other inflammatory skin conditions triggered by viruses. The exacerbation of pre-existing conditions and the mechanisms by which viruses can modulate the body's immune response raise critical questions that call for further exploration. The treatment regimens discussed throughout this review may not only benefit patients with scleroderma and morphea but also serve as valuable insights for guiding future research into therapies for other inflammatory conditions associated with viruses. This holistic approach to studying the interactions between viral infections and skin conditions can potentially lead to more effective and tailored treatments across a spectrum of dermatological presentations.

Conclusion

This study comprehensively reviewed the pathophysiology and clinical implications associated with inflammatory responses, specifically focusing on scleroderma and morphea, in relation to both COVID-19 vaccination and infection, including post-COVID syndrome. By analyzing the diagnostic nuances and potential therapies for these dermatological conditions along with other current knowledge, this review has revealed critical areas for future research. It has also highlighted gaps in the current literature, particularly regarding the intricate relationship between viruses and inflammatory skin conditions. This systematic review not only contributes to advancing our current understanding of the ramifications of COVID-19 on scleroderma and morphea but also reveals the need for ongoing research into the nuanced complexities that underlie the various inflammatory skin conditions influenced by COVID-19. It is imperative to continue exploring these interactions to provide more effective and tailored care to individuals affected by these conditions in the context of viral infections.

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