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Mini Review

Advancements and Innovative Therapies in Localized Scleroderma: A Mini-Review

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ABSTRACT

Localized Scleroderma (LS), also known as morphea, is a complex autoimmune disease that primarily impacts the skin and can extend to deeper tissues such as muscles and bones, significantly affecting quality of life. This mini-review explores recent research advancements in LS, focusing on its epidemiology, pathogenesis, clinical manifestations, and innovative treatments including Mesenchymal Stem Cell (MSC) therapy. Genetic, environmental, and immunological factors all contribute to Localized Scleroderma (LS), influencing the disease's progression through key cytokines involved in fibrosis. Additionally, advancements in diagnostic techniques, such as high-frequency ultrasound and MRI, have improved the ability to assess and monitor the disease. Traditional treatments include pharmacological interventions and phototherapy, while emerging therapies such as Mesenchymal Stem Cells (MSCs) therapy show promise in modulating immune responses and reducing fibrosis. This mini-review underscores the significant strides in understanding and treating LS, aiming to enhance therapeutic strategies and improve patient outcomes.

Keywords: Localized scleroderma; Mesenchymal stem cell therapy; Fibrosis; Autoimmune disease

INTRODUCTION

Localized Scleroderma (LS), also known as morphea, is a rare, chronic autoimmune disease characterized by the hardening and thickening of the skin and subcutaneous tissues [1]. LS can present in various forms, including plaque, linear, generalized, and deep morphea, each with distinct clinical features and implications [2]. The disease primarily affects the skin but can extend to underlying structures such as muscles and bones, leading to significant morbidity and impacting the quality of life. The etiology of LS remains unclear, but it is believed to involve a complex interplay of genetic, environmental, and immunological factors [3]. Genetic predispositions may contribute to the susceptibility, while environmental triggers such as infections, trauma, and certain medications may initiate or exacerbate the condition. Immunologically, LS is marked by an abnormal immune response where the body's immune system mistakenly attacks its tissues, leading to inflammation and fibrosis. This mini-review aims to discuss recent advancements, emerging research trends, and future prospects in the field of localized scleroderma. Additionally, we will delve into the potential of mesenchymal stem cell therapy to highlight innovative therapeutic approaches that hold promise for improving patient outcomes. By integrating these perspectives, we hope to provide a holistic overview of the advancements and future directions in LS research and treatment.

LITERATURE REVIEW

Epidemiology and demographics

The epidemiology and demographics of LS have been significantly elucidated through comprehensive research. Research reveals that the incidence and prevalence of LS vary across different geographic regions and ethnic populations. Notably, a higher prevalence is observed in Caucasian populations, with a pronounced female predominance [4]. LS typically manifests in the fifth decade of life, indicating a tendency for middle-aged onset. However, the disease is not

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exclusive to adults and can also affect children, particularly those between the ages of 2 and 14 [5,6]. Pediatric LS often follow a different disease course compared to adult-onset LS, necessitating tailored diagnostic and therapeutic approaches.

Pathogenesis and molecular mechanisms

A quality of the fibrotic process in LS is the excessive deposition of collage. Recent studies have highlighted the importance of key cytokines, such as Transforming Growth Factor-Beta (TGF-β), Inter Leukin-4 (IL-4), and Inter Leukin-13 (IL-13), in this process [7]. These cytokines have been identified as pivotal players in the pathogenesis of LS due to their roles in promoting fibroblast activation and extracellular matrix production. TGF-β, for instance, is a potent stimulator of collagen synthesis and has been shown to induce fibroblast differentiation into myofibroblasts, which are cells that produce large amounts of collagen. Similarly, IL-4 and IL-13 are involved in the activation and proliferation of fibroblasts, further contributing to the fibrotic changes observed in LS. Overall, these insights into the pathogenesis of LS have not only advanced the understanding of LS. By targeting the underlying mechanisms of endothelial dysfunction, immune dysregulation, and cytokine-mediated fibroblast activation, researchers hope to create more precise and effective therapeutic strategies that can significantly improve the lives of patients with LS.

Clinical manifestations and diagnosis

LS presents with a spectrum of clinical manifestations that can vary widely among patients. The disease can manifest in several forms, including plaque, linear, generalized, and deep morphea, each with distinct characteristics and clinical implications [2]. Plaque morphea is characterized by well-defined, localized patches of thickened skin. Linear morphea often affects the limbs or face and can lead to significant functional impairment and cosmetic concerns. Generalized morphea involves widespread skin thickening and can mimic systemic sclerosis in its severity. Deep morphea extends into the subcutaneous tissues and may affect underlying muscles and bones. Accurate diagnosis of LS requires a thorough clinical examination, supported by advanced imaging techniques and histopathological analysis. Recent advancements in imaging, such as high-frequency ultrasound and Magnetic Resonance Imaging (MRI), have greatly enhanced the ability to assess disease activity and monitor treatment response [8]. Ultrasound allows for the non-invasive evaluation of skin thickness and tissue characteristics, while MRI provides detailed images of deeper tissues and can help differentiate between active inflammation and established fibrosis. Histopathological examination remains the gold standard for confirming the diagnosis, revealing characteristic features such as dermal thickening, collagen deposition, and inflammatory cell infiltrates. These advancements in understanding the epidemiology, pathogenesis, and clinical manifestations of LS have paved the way for more precise diagnostic criteria and targeted treatment strategies.

DISCUSSION

Pharmacological interventions

Pharmacological treatment for LS remains a cornerstone in managing moderate to severe cases, with Methotrexate (MTX) and corticosteroids being the primary agents utilized [9]. MTX, a folate antagonist, exerts its effects by inhibiting dihydrofolate reductase, which leads to a suppression of DNA synthesis and cell replication. In the treatment of LS, MTX is particularly valued for its ability to modulate cytokine cascades, thereby reducing inflammation and halting the progression of fibrosis. Studies have shown that MTX can effectively reduce skin thickening and improve clinical outcomes when used as a monotherapy or in combination with corticosteroids. Corticosteroids, such as prednisone, are potent anti-inflammatory agents that inhibit multiple inflammatory pathways [10]. Their rapid action in reducing inflammation makes them indispensable in the initial management of LS, especially in acute or rapidly progressing cases. When combined with MTX, corticosteroids enhance treatment efficacy, providing a synergistic effect that results in better control of disease activity and a quicker therapeutic response [10]. This combination therapy has been found to not only improve skin lesions but also prevent the recurrence of fibrosis, making it a preferred treatment regimen for many clinicians.

Phototherapy

Phototherapy has emerged as a valuable treatment modality for LS, with UVA1 radiation being particularly effective. High-dose UVA1 phototherapy works by penetrating deep into the skin, where it exerts immunomodulatory and anti-fibrotic effects [11]. UVA1 radiation helps to soften sclerotic plaques, reduce skin thickness, and improve elasticity. This treatment modality has been supported by numerous studies demonstrating its efficacy in both adult and pediatric populations. In adults, UVA1 phototherapy has shown significant improvements in skin flexibility and reduction in fibrotic lesions. In children, it offers a non-invasive treatment option that can be tailored to the severity of the disease, making it a versatile and effective tool in the management of LS.

Mesenchymal Stem Cells (MSCs) therapy

Mesenchymal Stem Cell (MSCs) therapy represents a promising frontier in the treatment of LS. MSCs possess unique immunomodulatory, anti-inflammatory, and anti-fibrotic properties that make them ideal candidates for therapeutic intervention in autoimmune and fibrotic diseases [12]. MSCs can be sourced from various tissues, including bone marrow, adipose tissue, and umbilical cord blood, each offering distinct advantages in terms of availability and potency. These stem cells have the remarkable ability to differentiate into various cell types, including endothelial cells, which are directly involved in the pathological processes of LS. One of the key mechanisms by which MSCs exert their therapeutic effects is through the inhibition of T cell proliferation [13]. In LS and other autoimmune diseases, T cells play a significant role in driving

inflammation and fibrosis. MSCs modulate the immune response by promoting the transition of T cells from a pro-inflammatory state to an anti-inflammatory state. This shift is crucial in reducing the ongoing inflammatory processes that contribute to tissue damage and fibrosis. Additionally, MSCs stimulate the production of regulatory T cells (Tregs), which are essential for maintaining immune homeostasis and preventing autoimmune responses [14]. Tregs help suppress the activity of T cells that target the body's own tissues, thereby mitigating the autoimmune component of LS. Moreover, MSCs secrete a variety of bioactive molecules, including cytokines, growth factors, and extracellular vesicles, which have potent anti-inflammatory and anti-fibrotic effects [15]. These secreted factors can inhibit the activation of fibroblasts, the primary cells responsible for producing excessive collagen and extracellular matrix components in LS. By modulating fibroblast activity, MSCs help to prevent the progression of fibrosis and promote the remodeling of affected tissues. Preclinical studies using animal models of LS have demonstrated the significant efficacy of MSC transplantation in reducing skin fibrosis and improving vascular function [16]. In these animal models, MSCs have been shown to decrease the thickness of fibrotic lesions, reduce collagen deposition, and enhance blood flow to the affected areas. These beneficial effects are attributed to the combined immunomodulatory, anti-inflammatory, and pro-angiogenic properties of MSCs. The success of these preclinical studies has paved the way for clinical trials aimed at evaluating the safety and efficacy of MSC therapy in patients with scleroderma. Early results from clinical trials are promising, indicating potential benefits of MSCs therapy in reducing disease severity and improving the quality of life for patients with scleroderma [17,18]. These trials have reported improvements in skin elasticity, reduction in the extent of fibrotic lesions, and enhanced functional outcomes in treated patients. Furthermore, MSC therapy has been associated with a favorable safety profile, with minimal adverse effects reported in most studies. Further trials should aim to optimize the sourcing, preparation, and delivery methods of MSCs to maximize their therapeutic efficacy. In addition to traditional MSC transplantation, innovative approaches such as the use of MSC-derived exosomes and engineered MSCs are being explored [19,20]. MSC-derived exosomes are small extracellular vesicles that carry bioactive molecules and have shown similar therapeutic effects as their parent cells. Engineered MSCs, which are genetically modified to enhance their therapeutic properties, represent another exciting avenue of research. These advanced strategies hold the potential to further enhance the efficacy and specificity of MSC therapy for scleroderma and other fibrotic diseases.

CONCLUSION

LS is a complex autoimmune disease that primarily affects the skin and subcutaneous tissues but can extend to muscles and bones, leading to significant morbidity. Recent advancements in understanding the epidemiology, pathogenesis, and clinical manifestations of LS have clear the way for more precise diagnostic criteria and targeted treatments. Pharmacological interventions and phototherapy have shown effectiveness in the treatment of LS. MSCs therapy offers promising potential due to their immunomodulatory and anti-fibrotic properties, with early clinical trials indicating benefits in reducing disease severity and improving quality of life. Future research will focus on optimizing MSC therapy and exploring innovative approaches to enhance its efficacy, paving the way for improved therapeutic strategies for LS.

REFERENCES

1. Careta MF, Romiti R. Localized scleroderma: Clinical spectrum and therapeutic update. An Bras Dermatol. 2015;90(1):62-73.
2. Bielsa Marsol I. Update on the classification and treatment of localized scleroderma. Actas Dermosifiliogr. 2013;104(8):654-666.
3. Fett N, Werth VP. Update on morphea: Part I. Epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol. 2011;64(2): 217-228.
4. Li SC, Higgins GC, Chen M, Torok KS, Rabinovich EC, Stewart K, et al. Extracutaneous involvement is common and associated with prolonged disease activity and greater impact in juvenile localized scleroderma. Rheumatology (Oxford). 2021;60(12):5724-5733.
5. Christen-Zaech S, Hakim MD, Afsar FS, Paller AS. Pediatric morphea (localized scleroderma): Review of 136 patients. J Am Acad Dermatol. 2008;59(3):385-396.
6. Zulian F, Athreya BH, Laxer R, Nelson AM, de Oliveira SKF, Punaro MG, et al. Juvenile localized scleroderma: Clinical and epidemiological features in 750 children. An international study. Rheumatology (Oxford). 2006;45(5):614-620.
7. Muruganandam M, Ariza-Hutchinson A, Patel RA, Sibbitt WL, Jr. Biomarkers in the pathogenesis, diagnosis, and treatment of systemic sclerosis. J Inflamm Res. 2023;16(2):4633-4660.
8. Idzior M, Sotniczuk M, Michalski E, Gietka P, Sudoł-Szopińska I. Ultrasonography, MRI and classic radiography of skin and MSK involvement in juvenile scleroderma. J Ultrason. 2021;20(83):e311-e317.
9. Badea I, Taylor M, Rosenberg A, Foldvari M. Pathogenesis and therapeutic approaches for improved topical treatment in localized scleroderma and systemic sclerosis. Rheumatology (Oxford). 2009;48(3):213-221.
10. Weibel L, Sampaio MC, Visentin MT, Howell KJ, Woo P, Harper JI. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. Br J Dermatol. 2006;155(5):1013-1020.
11. Stege H, Berneburg M, Humke S. High-dose UVA1 radiation therapy for localized scleroderma. J Am Acad Dermatol. 1997;36(6): 938-944.
12. Farge D, Loisel S, Lansiaux P, Tarte K. Mesenchymal stromal cells for systemic sclerosis treatment. Autoimmun Rev. Mar 2021;20(3): 102755.
13. Cras A, Farge D, Carmoi T, Lataillade JJ, Wang DD, Sun L. Update on mesenchymal stem cell-based therapy in lupus and scleroderma. Arthritis Res Ther. 2015;17(1):301.
14. Cipriani P, Di Benedetto P, Liakouli V, Papa BD, Padova MD, Ianni MD, et al. Mesenchymal Stem Cells (MSCs) from Scleroderma Patients (SSc) preserve their immunomodulatory properties although senescent and normally induce T regulatory cells (Tregs) with a functional phenotype: implications for cellular-based therapy. Clin Exp Immunol. 2013;173(2):195-206.
15. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem. 2006;98(5):1076-1084.
16. Wang HC, Sun ET, Zhao RC, Chen B, Han Q, Li N et al. Adipose-derived stem cells attenuate skin fibrosis and improve fat retention of a

localized scleroderma mouse model. Plast Reconstr Surg. 2023;151(1):97-107.

17. Keyszer G, Christopeit M, Fick S, Schendel M, Taute BM, Behre G, et al. Treatment of severe progressive systemic sclerosis with transplantation of mesenchymal stromal cells from allogeneic related donors: Report of five cases. Arthritis Rheum. 2011;63(8): 2540-2542.
18. Zhang H, Liang J, Tang X, Wang D, Feng X, Wang F, et al. Sustained benefit from combined plasmapheresis and allogeneic mesenchymal stem cells transplantation therapy in systemic sclerosis. Arthritis Res Ther. 2017;19(1):165-167.
19. Wang L, Li T, Ma X, Li Y, Li Z, Li Z, et al. Exosomes from human adipose-derived mesenchymal stem cells attenuate localized scleroderma fibrosis by the let-7a-5p/TGF-βR1/Smad axis. J Dermatol Sci. 2023;112(1):31-38.
20. Jibing C, Weiping L, Yuwei Y, Bingzheng F, Zhiran X. Exosomal microRNA-Based therapies for skin diseases. Regen Ther. 2024;25:101-112.