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REVIEW ARTICLE **OPEN ACCESS**

Brief Review on Morphea

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ABSTRACT

Researchers have also found that morphea (M), which is also called "localized scleroderma, is a long-lasting inflammatory condition of the connective tissues that can happen to both kids and adults and show up in different ways". Additionally, studies have shown that this disorder is characterized by "swelling and scarring of the skin and the soft tissue beneath it. In some cases, it can also affect the fascia, muscles, bones, and central nervous system". In addition to this, studies have also shown that "inflammation and fibrosis of the skin and underlying soft tissue are the hallmarks of this condition". Furthermore, studies have also shown that it is essential to precisely diagnose disease activity and to promptly begin the right treatment in order to prevent additional damage. In addition to this, studies have also concluded that the advancement of the disease may have long-term cosmetic and functional ramifications. Studies have also shown that the treatment focuses mostly on the use of corticosteroids and methotrexate. On the other hand, their toxicity is limited, especially when utilized for a lengthy period of time during the course of their lifetime. Hence, it is difficult to treat the disease and/or relapses of morphea with corticosteroids and methotrexate on their own. Thus, in our review, we have discussed M in terms of clinical feature, diagnosis, differential diagnosis, general overview, and treatment aspect.

Key words: *M , clinical feature, diagnosis, differential diagnosis, general overview, treatment aspect.*

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INTRODUCTION

Studies have concluded that "M, also known as localized scleroderma, is a rare inflammatory connective tissue illness that mostly affects children between the ages of 2 and 14 years".[1,2,3] Various studies have concluded that it is also more common in women. Studies concluded that "it is characterized by the presence of inflammatory patches and/or bands of thicker skin on the head and neck area, trunk, and extremities".[4] Furthermore, studies have concluded that , "based on its size and depth, fibrosis can be broken down into five main groups: limited, generalized, linear, deep, and mixed".[5] Additionally, studies concluded that , "there are also several subgroups, such as plaque-type, pansclerotic, en coup de sabre, and so on". Studies have shown that "even though it is thought to be a disease that only affects the skin, some subtypes are linked to symptoms that show up in other parts of the body, like headaches, migraines, seizures, epilepsy in the central nervous system, and eye inflammation in the uvea".[4] Studies have concluded that these symptoms may be seen in people who have psoriasis but do not have psoriasis on their skin. Studies have also found that "they can cause severe deformities (like persistent hyperpigmentation and skin atrophy), functional limitations (like joint contractures), and eye and brain issues".[6,7] Studies have concluded that even though there are signs outside of the skin, morphea should not be confused with systemic sclerosis (SSc).[4] Studies have found that "certain things (like infections, medications, or trauma) may cause vascular and immune system problems in people who are genetically more likely to get the disease". However, studies have concluded that the "exact cause of the disease is still unknown". Studies have concluded that, "the activation of T-cells and the release of cytokines linked with interferon-β (IFN-β) are implicated, and this leads to the activation of inflammatory and profibrotic pathways, which ultimately results in an excessive amount of collagen formation". [6,8,9,10,11] Thus, in our review we have discussed about morphea.

GENERAL OVERVIEW

Studies have found that "M is a relatively uncommon condition that affects the connective tissue".[12,13] Studies have also concluded that "it is characterized by inflammation and has a low occurrence rate, with only a few new cases reported each year". In this, according to studies, "majority of cases occur in adults,

while juvenile localized scleroderma has an estimated annual incidence rate of 3.4–9 cases per million children per year".[14,12,15,16] Studies have also shown that "it is worth mentioning that morphea is more prevalent in children compared to SSc, with an incidence rate that is 6–10 times higher. However, in adults, the annual incidence rates of SSc are similar or even higher".[16,17,18] In adults, studies have shown that the plaque-type morphea is the most frequently observed variant, with the generalized variant being the next most common. However, studies concluded that "in children, the linear form of morphea is the prevailing type". [1,2, 12, 19] According to a study, "it was found that a significant number of children (22%) and adults (11%) diagnosed with morphea had a family history of connective tissue or autoimmune diseases in their close relatives".[2] In addition to this, studies have also shown that, 22% of cases involving morphea in children, this is reported. Furthermore, studies have concluded that , "it's worth noting that the generalized and mixed types show the most significant correlation with autoimmune diseases that tend to be hereditary".[20] Studies have also found that congenital localized scleroderma, which takes an average of 3.9 years to be diagnosed, is a rare and underappreciated form of the disease. [21] A study of people who had been diagnosed with juvenile localized scleroderma found that 0.8% of those cases had skin lesions at birth and that girls were twice as likely as boys to have this type of the disease.[21] Additionally, studies have also found that the en coup de sabre subtype was the most common clinical presentation.[21, 22,23]

CLINICAL FEATURE

Studies have also found that "M most often manifests as macules or plaques with a diameter of a few centimeters; however, it may also manifest as bands, as guttate lesions, or in nodules". [23] In addition, studies have found that it is characterized by the "skin and subcutaneous tissues becoming thicker and harder because too much collagen accumulates beneath the skin". [24] According to studies, "the mixed form of M, in which diverse morphologies of skin lesions are present in the same person, is not included in this categorization system since it is not considered to be a true type of M". [1]

PATHOPHYSIOLOGY [20]

Studies have concluded that their are variety of factors includes which plays an important role in the development of M like genetic, environmentalfactors such as infections, skin trauma ,autoimmune dysregulation with abnormal cytokine productionand /or vascular dysfunction. In general according to studies there are 3 phases in the process of patthogenesis ie. early inflammatory phase,fibrotic /sclerotic phase and atrophic phase.[Figure 1]

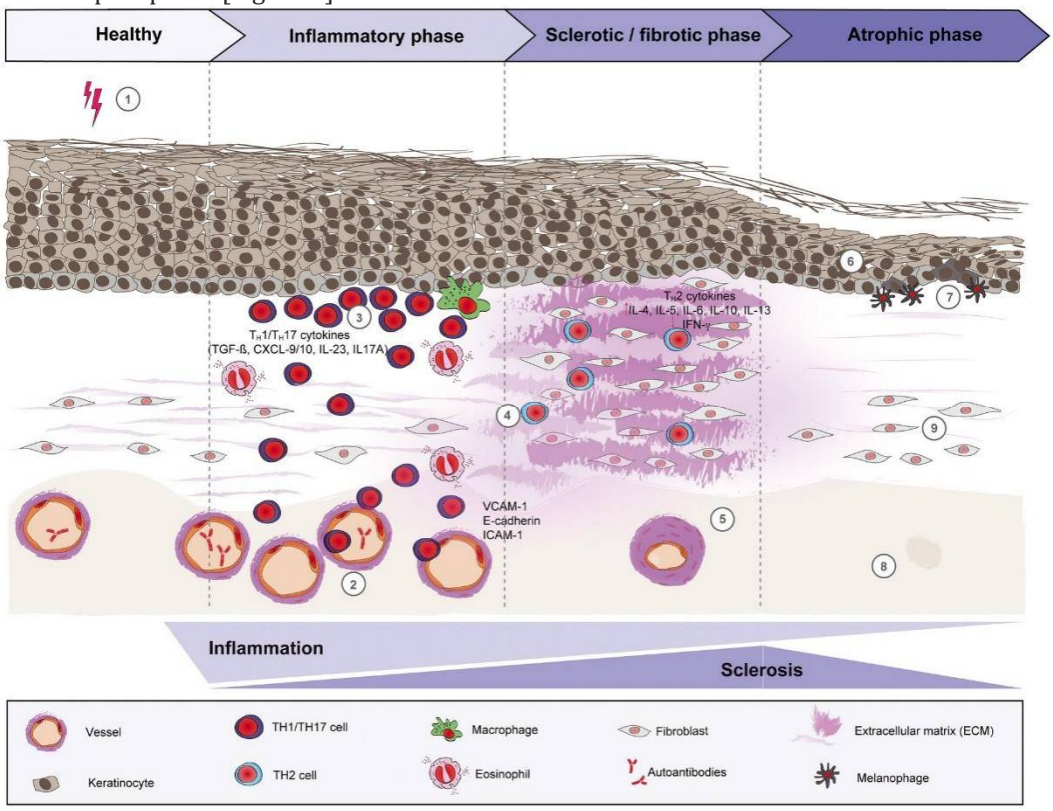

Fig. 1: Schematic Overview (Pathogenesis)

Studies have concluded that, according to the knowledge that is currently available, the etiology of morphea may be divided into three distinct phases: the early inflammatory phase, the sclerotic/fibrotic phase, and the late atrophic phase. Thus figure1 shows that there are 3 phases are listed in this order:
1 = T cell-driven skin inflammation, as well as plasma cells and eosinophils around the vessels, adnexal structures, and dermis, may be activated in patients who are genetically sensitive to environmental stresses like radiation, skin trauma, and infections. During the inflammatory stage, the severe endothelial damage that was generated as a direct consequence would lead to the overexpression of adhesion molecules such as E-cadherin and VCAM-1.
2 = This will bring in TH1 cells that cause inflammation and TH17 cells that stop it. It will also bring in cytokines like CXCL-9/10, TGF-ß, IL-23, and IL-17A, which will turn on fibroblasts.
3 = After that, a change toward a more TH2-driven response would allow the recruitment of T cells that can produce cytokines that promote fibrosis, such as IL-4, IL-6, and TGF-ß. This would follow from the preceding point.
4 = Because of this, the chance of getting sclerosis goes up when there are hyalinized, tight collagen bundles in the dermis and when there aren't many sweat glands or blood vessels, since blood vessels have thicker walls and smaller openings. Additionally, the risk of sclerosis increases when there are fewer sweat glands and blood vessels.
5= During the latter phases of sclerosis, atrophy progressively increases. Within the epidermis, the thickness will decrease
6= Basal keratinocytes will become colored because of the melanophages that are present below. Additionally, there will be an increase in the number of melanophages.
7= Loss of blood vessels, inflammatory cells, and skin appendages all occur simultaneously.
8= Loss of skin appendages, blood vessel
9= Inflammatory cell [20]

INVESTIGATIONS [20]

1. HISTOPATHOLOGY

Studies have also found that the biopsy needs to be done at the right depth because some types of morphea can affect the subcutis as well as the fascia and muscle below it.[25] However, normal histopathology cannot tell the difference between the different types of morphea or between them and SSc.[26] Studies have concluded that, despite this, it may provide information on the state of the patient's sickness. Early skin lesions show these features: (i) thick collagen bundles in the reticular dermis that run parallel to the skin surface; (ii) dense inflammatory infiltrates made up of lymphocytes, eosinophils, plasma cells, and histiocytes between the collagen bundles, in the perivascular and periadnexal areas; and (iii) an epidermis that is normal or atrophic on top. Later, fibrotic skin lesions become less inflammatory and avascular, with thicker blood vessel walls and smaller lumens. Collagen bundles become thick, dense, and highly eosinophilic, and sweat glands become few or nonexistent. Additionally, fibrotic skin lesions are characterized by the presence of thicker collagen bundles. Additionally, a significant increase in the collagen bundles' thickness serves to distinguish fibrotic skin lesions.[20]

2. LABORATORY TEST

According to studies, although there are currently no diagnostic tests available for morphea, it is recommended to perform baseline investigations, particularly when considering systemic treatment. It is recommended to conduct a full blood count, kidney and liver function tests, creatine kinase (if myositis is suspected), rheumatoid factor (if arthritis is suspected), and C-reactive protein (CRP) tests.[26] In the active stages of linear morphea, there are certain indicators that can be observed. These include hypergammaglobulinemia, elevated CRP levels, and eosinophilia. It is worth noting that eosinophilia is also seen in the generalized type of morphea.[27,28,29,30] Additionally studies have concluded that when aldolase levels are higher, it can be associated with joint contractures. On the other hand, increased creatine kinase levels are connected to muscle atrophy and the shortening of extremities.[31]

3. RADIOLOGY

a. MRI

Additionally, research has found that all people with morphea in the face, head, or neck should have an MRI of the brain with contrast, even if they don't have typical neurological symptoms like headaches, migraines, seizures, or hemiparesis.[26] Studies have concluded that it is interesting to note that a significant number of patients with morphea lesions on the head or face do not show any neurological symptoms, despite the presence of intracranial abnormalities on MRI scans.[32] Studies have concluded that some possible findings from imaging studies may include white matter and leptomeningeal enhancements, dystrophic calcifications, sulcal crowding, cerebral atrophy, and even CNS vasculitis[32,33].

b. Ultrasonography

Additionally, research has found that in the beginning, lesions have a hypoechogenic appearance, but as they advance and become fibrotic, they take on a hyperechogenic appearance.[35] Studies have concluded that more blood flow and higher sensitivity to sound waves under the skin are signs of active lesions, which suggests that color Doppler may help doctors figure out what's wrong.[35]

c. RCM &OCT

Researchers have found that new imaging methods such as reflectance confocal microscopy (RCM) and optical coherence tomography (OCT) might make it possible to diagnose inflammatory skin diseases like morphea in real time and without surgery.[36,37] Studies have concluded that while RCM only evaluates the skin's horizontal sections, OCT examines both the horizontal and vertical sections to determine its morphology. In addition, sclerodermiform diseases are well-suited to high-definition optical coherence tomography (HD-OCT) since it permits a more in-depth evaluation of the skin. Studies have concluded that as shown by HD-OCT imaging, morphea is characterized by a persistent darkening (hyporefractiveness) of the dermis. Studies have concluded that dermoscopy and histopathology both corroborate that this blackness indicates the presence of sclerosis.[38]

d. Thermography

Researchers have found that infrared thermography may aid in the identification of active morphea variations, with a sensitivity and specificity of 80.7% and 86.3%, respectively.[39] Studies have concluded that the clinical ratings for erythema and skin atrophy were also shown to be positively correlated with them. However, this strategy has a number of limitations, and it may not be suitable for clinical application with morphea just yet. Further study is required on infrared testing thermography for morphea patients.[20]

DIAGNOSIS [40,41]

1. "M-lichen sclerosus et atrophicus
2. Generalized M
3. M Profunda
4. Pansclerotic M
5. Linear Scleroderma
6. Frontal Linear Scleroderma
7. Atrophoderma of Pasini & Pierini"

DIFFERENTIAL DIAGNOISIS [20]

1. "Lichen Sclerosus
2. Granuloma Annulare
3. Cutaneoous Mastocytosis
4. Erythema Cronicum Migrans
5. Porokeratosis Mibelli
6. Mycosis Fungoides
7. Vitiligo
8. Annular Lichenoid Dermatitis of youth (ALDY)
9. Morpheaform injection –site reactions
10. Scarring
11. Acrodermatitis chronica atrophican
12. Lipodermatosclerosis
13. Carcinoma en cuirasse
14. Sclerosing congenital melanocytic nevus/ connective tissue nevi
15. Morpheaform basal cell carcinoma
16. Necrobiosis Lipoidica
17. Pretibial Myxedema
18. Post-inflammatory hyperpigmentation
19. Erythema Discromicum Perstan
20. Cafe-au-lait spot
21. Systemic Sclerosis(Scleroderma)
22. Scleredema
23. Scleromyxedema
24. Chronic graft-versus –host disease
25. Porphyria cutanea tarda
26. Primary Systemic Fibrosis

27. Morpheaform Sarcoidosis
28. Paraneoplastic scleroderma-like syndrome
29. Phenylketonuria
30. Genetic Disorder
31. Panniculitis
32. Localized Lipodystrophy
33. Steroid-induced atrophy
34. Sclerosing nevus
35. Lupus erythematous profundus
36. Focal dermal Hypoplasia
37. Reflex sympathetic dystrophy
38. Diabetic Cheiroartropathy
39. Eosinophilic Fascitis
40. Panniculitis"

TREATMENT [42]

"Over the years, numerous treatments have been experimented with for M, including the use of topical, intra-lesional, and systemic corticosteroids. Antimalarials like hydroxychloroquine or chloroquine have been utilized. Various immunomodulators, according to studies, including methotrexate, topical tacrolimus, and penicillamine, have been tested. Studies have also shown that children and teenagers with active morphea (linear scleroderma, generalized morphea, and mixed M: linear and circumscribed) may see more significant improvement in disease activity or damage when treated with oral methotrexate and prednisone compared to those who receive placebo and prednisone. [28] In addition to this, studies have laso shown that, prescription vitamin D has been found effective by some individuals. UVA light, with or without psoralens, has also been explored as a potential treatment option. UVA-1, a wavelength of UVA light that is more focused, has the ability to reach the deeper layers of the skin. This is believed to have two effects on morphea plaques: it may suppress the immune system through UV light exposure, or it may stimulate enzymes that naturally break down the collagen matrix in the skin, similar to the effects of sun exposure". [42]

CONCLUSION

We have come to the conclusion that one of the most important steps is to determine the disease activity by using the most recent validated clinical ratings. A delayed diagnosis or an inaccurate evaluation of the severity may lead to a delay in proper treatment, which in turn may lead to physical and functional limitations as well as a decline in quality of life. Starting enough systemics is key to controlling the disease and limiting any harm it may cause. In addition to this, childhood morphea has been linked to a more severe disease course as well as an increased risk of recurrence, the latter of which may occur even after many years of being in remission. In addition, there are certain cases that do not respond to the treatments that are now available, such as methotrexate, systemic corticosteroids, and mycophenolate mofetil. On the other hand, new developments in our knowledge of the pathophysiology of morphea have discovered novel targets. Thus, it may be possible to use these new targets to stop the early stages of inflammation so that fibrosis and atrophic changes don't happen. The disease may still need combination therapies as well as extended follow-up periods.

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