SKIN

BRIEF ARTICLE

A Case of Generalized Morphea in the Setting of Aplastic Anemia

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ABSTRACT

Background: Morphea is a rare sclerosing disorder characterized by the formation of erythematous to violaceous lesions and sclerotic plaques on the skin that can extend to the reticular dermis and subcutaneous tissue. This condition may be associated with pain, pruritus, and limitations in range of motion, causing significant disruption in patients' quality of life. Similar sclerosing disorders, such as eosinophilic fasciitis and systemic sclerosis, have been associated with hematologic diseases like aplastic anemia (AA). However, few reports of morphea in association with AA have explored this relationship.
Case presentation: A 29-year-old woman with a history of AA presented with pruritic, indurated hyperpigmented plaques on her lower extremities. Her past medical history included congenital aortic stenosis and focal epilepsy. A skin biopsy was consistent with morphea. A concurrent bone marrow biopsy confirmed persistent hypocellularity consistent with AA.
Conclusion: This case highlights a potential immunologic link between morphea and AA given that both diseases involve dysregulated T cell-mediated immune responses. We explore a potential immunologic connection between the two conditions, including the role of chemokines, such as CXCL10, in their pathogenesis. Additionally, we discuss important considerations for physicians when evaluating patients with morphea.

INTRODUCTION

Morphea, also known as localized scleroderma, is a rare sclerosing disorder that involves a complex relationship between immune dysregulation, genetics, and environmental factors.[1] Morphea presents as erythematous to violaceous lesions and sclerotic plaques that can be associated with pain, pruritus, and limitations in range of motion. Sclerosis may extend to the reticular dermis, and even to subcutaneous tissue. While the precise immunopathogenesis underlying morphea remains uncertain, it is generally attributed to autoimmune processes resulting in sclerosis of the skin.[1] Sclerosing disorders like eosinophilic fasciitis and systemic sclerosis are known to be associated with various systemic diseases, including hematologic malignancies and plasma cell dyscrasias.[2] Additionally, eosinophilic fasciitis has been reported in conjunction with aplastic anemia (AA).[3] To the best of our knowledge, only two cases of morphea associated with AA have been reported in the literature.[4,5] We present the case of a 29-year-old female who was

subsequently diagnosed with morphea following a diagnosis of AA, and discuss important considerations for physicians evaluating a diagnosis of morphea.

CASE PRESENTATION

A 29-year-old female presented to our dermatology clinic in April 2024 with skin changes for the past several months on her lower extremities, accompanied by pruritus and inflammatory arthritis. The patient reported a history of AA since 2015, which was diagnosed via a bone marrow biopsy following pancytopenia and managed by a hematologist. She also reported a history of focal epilepsy disorder treated with lamotrigine and brivaracetam, and a diagnosis of congenital aortic stenosis that was treated in infancy. Physical examination revealed hyperpigmented patches with notable background induration on bilateral lower extremities (**Figure 1**) and normal nailfold capillary loops. Blood work at the time revealed a positive antinuclear antibody (1:320) and negative results for antibodies against Scl-70, double-stranded DNA (dsDNA), cyclic citrullinated protein (CCP), and rheumatoid factor. A skin biopsy of the affected areas revealed deep dermal sclerosis, clinically consistent with a diagnosis of morphea (**Figure 2**). A bone marrow biopsy from May 2024 following persistent anemia and leukopenia demonstrated a hypocellular bone marrow consistent with a diagnosis of AA. At the time of our first evaluation, the patient had been on hydroxychloroquine 200 mg twice daily since 2021 for seronegative arthritis.

DISCUSSION

Morphea is a rare fibrosing disorder of the skin widely believed to be a result of immune dysregulation.[1] Increased serum levels of cytokines associated with the type 2 helper (Th2) inflammatory response, such as interleukin (IL)-4, have been detected in patients with morphea, which is thought to result in an upregulation in the production of transforming growth factor beta (TGF-β).[1] TGF-β works to stimulate fibroblasts resulting in the synthesis of collagen and extracellular matrix protein. The role of TGF-β in the pathogenesis of morphea has not been clearly defined. One study found patients with morphea and systemic sclerosis to exhibit decreased regulatory T-cells, TGF-β, and IL-10 in skin samples, as well as reduced serum TGF-β and IL-10 levels, which play important roles in the regulation of the immune response.[6] Another study by Ayvaz Celik *et al*. found elevated serum levels of TGF-β, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FBF) in morphea patients compared to healthy controls.[7] It has been postulated that there is a Th1/Th17/Th2 imbalance in the progression from an early inflammatory phase to a later sclerotic phase in morphea.[1] Additional studies have also found upregulation of CXCR3 ligands, CXCL9 and CXCL10, which have been implicated in the inflammatory stage of fibrosis in morphea.[1] It was found that through binding of their shared receptor, CXCR3, the above chemokines could induce T cell migration, and may play a role in extracellular formation and collagen deposition.[1] These chemokines have been long thought to be associated with Th1 cell-mediated autoimmune diseases. Importantly, CXCL10 has also been implicated in the pro-inflammatory process of AA, which has been described as a T cell-mediated immune dysfunction that results in the apoptosis of hematopoietic stem/progenitor cells (HSPCs).[8] CXCL10 and interferon gamma (IFN-γ) induce a signaling cascade for the recruitment of inflammatory cells and killing of HSPCs.[9] Further exploring this association

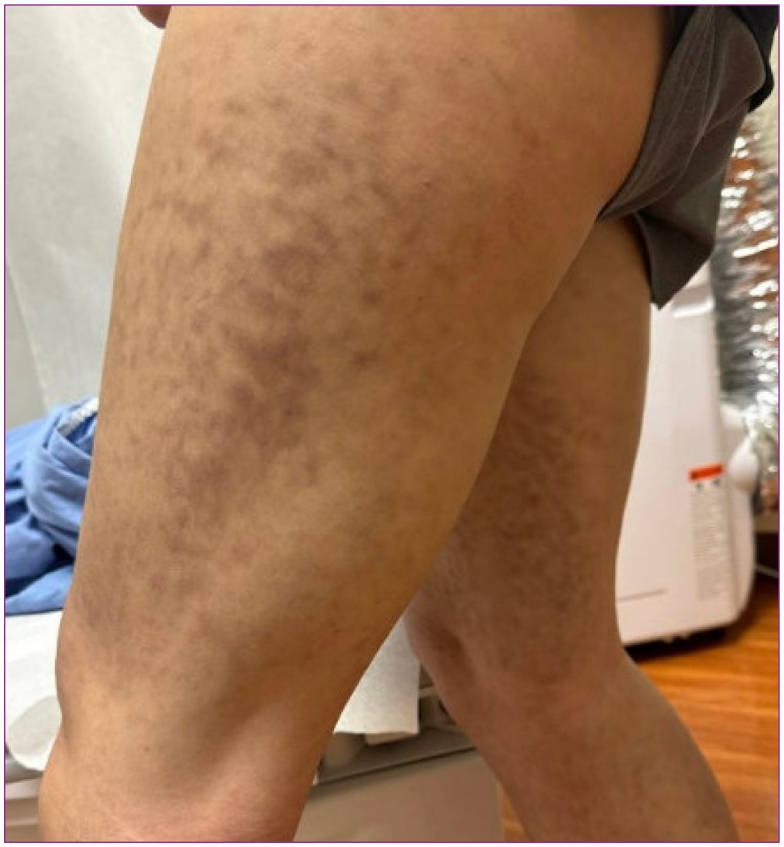

Figure 1. Physical examination demonstrating widespread violaceous and indurated patches throughout bilateral lower extremities.

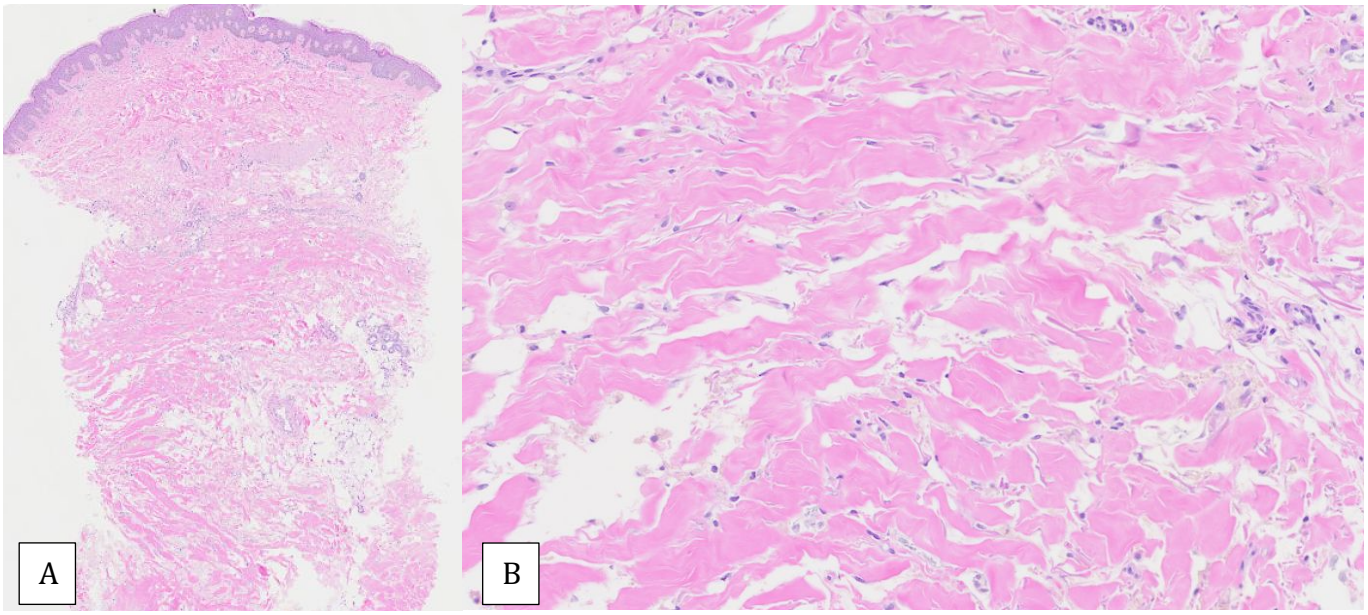

Figure 2. Skin punch biopsy stained with hematoxylin and eosin (H&E). **A)** Histologic findings consistent with morphea demonstrate a sparse lymphocytic infiltrate, decreased adnexal structures, and dense sclerotic collagen bundles down to the subcutaneous fat (4x magnification). **B)** Collagen fibers are eosinophilic and thickened (20x magnification).

may help elucidate a common pathway in the pathogenesis of AA and morphea via CXCR3 and IFN-γ.

As of the writing of this report, the association between AA and morphea has been described in two case reports.[4,5] Morphea has also been linked to various other Th1-mediated immune-mediated disorders, including psoriasis, vitiligo, and alopecia areata.[10] AA has also been previously found in association with systemic sclerosis and eosinophilic fasciitis.[2] Given the similarities between morphea and eosinophilic fasciitis, it is possible the associations between morphea and AA may be underreported. In documented cases, eosinophilic fasciitis is typically diagnosed months after the initial diagnosis of AA.[3] In our case, AA was diagnosed prior to the diagnosis of morphea, though the presence of morphea may have preceded the development of AA unbeknownst to the patient. In the previous case reports, morphea preceded the diagnosis of AA, suggesting a mutual association with an autoimmune syndrome.[4,5] Furthermore, exploration of this association may reveal additional insight into the pathophysiology of morphea and its relationship to AA. Physicians treating patients with morphea may consider hematologic consultation to rule out concomitant AA in the appropriate clinical setting. Immunomodulatory treatment options targeting their possible shared pathway may address aspects of both diseases when presenting in tandem.

Conflict of Interest Disclosures: Dr. Jordan Talia has served as a consultant for Abbvie, Arcutis Biotherapeutics, Bristol-Meyers Squibb, Calliditas Therapeutics, Johnson & Johnson, Galderma, Leo Pharma, Navigator Medicines, Novartis, Primus Pharmaceuticals, Sanofi Genzyme, Stifel Financial, and UCB. He serves as an investigator for LEO Pharma and Sanofi. Dr. Graham Litchman has served as a consultant for Abbvie, Arcutis Biotherapeutics, Amgen, Blueprint Medicines, Boehringer Ingelheim, Bristol-Meyers Squibb, Castle Biosciences, Galderma, Novartis, Pfizer, Sanofi Genzyme, Scibase, Sensus, and UCB. He serves as an investigator for Abbvie, AnaptysBio, ASLAN Pharmaceuticals, Galderma, Incyte, Moonlake Immunotherapeutics, Palvella Therapeutics, RAPT Therapeutics, Regeneron Pharmaceuticals, Sanofi, Sun Pharma, Takeda Pharmaceuticals. Gabriela Soto-Canetti has no conflicts of interest to disclose.

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