Interferon beta-1a–induced morphea

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INTRODUCTION

Interferon beta-1a (IFN-β1a) is a cytokine therapy used in the treatment of relapsing-remitting multiple sclerosis. The most common adverse injection site reactions include local erythema, pain, and induration.[1] Other less frequently encountered reactions include vascular thrombosis, ulceration, panniculitis, and lipoatrophy.[1] More recently, IFN-β rarely has been noted to be associated with sclerosing skin disorders including limited and diffuse systemic sclerosis; however, the development of morphea has not been reported.[2] Here we describe a patient with multiple sclerosis who had woody induration clinically and histologically consistent with morphea at the sites of subcutaneous IFN-β1a injections.

Abbreviations used:

IL-4:	Interleukin 4
IFN-β:	Interferon beta
IFN-β1a:	Interferon beta-1a
MS:	Multiple sclerosis
SSc:	Systemic sclerosis
Th2:	T helper 2

CASE REPORT

A 52-year-old African American woman with a history of multiple sclerosis (MS) presented to the dermatology clinic for evaluation of "firmness and skin discoloration" at IFN-β1a injection sites. Five years previously she began IFN-β1a therapy, and approximately 6 months after initiation she noted the gradual onset of firmness, skin depression, and hyperpigmentation confined to the injection sites. Over the last several years, she noted progression and worsening of the induration and hyperpigmentation. Therefore IFN-β1a therapy was discontinued, and she started taking oral dimethyl fumarate approximately 1 year before presentation. Interestingly, the woody induration continued to progress despite cessation of interferon treatment.

Physical examination was remarkable for depressed, indurated, bound-down, hyperpigmented plaques involving her upper anterior thighs, upper arms, and abdomen (Fig 1). The rest of the cutaneous examination findings were unremarkable. A punch biopsy was performed from the right thigh, and histopathologic evaluation found thickening and homogenization of collagen bundles extending into the subcutaneous fat, paucity of adnexal structures, and a lymphoplasmacytic infiltrate in the deep reticular dermis (Fig 2). The histologic features were most consistent with the inflammatory stage of morphea. Laboratory evaluations, including erythrocyte sedimentation rate, complete blood count, basic metabolic panel, creatine kinase level, antinuclear antibody, antitopoisomerase I, and anticentromere antibody were within normal limits. The clinicopathologic features were most consistent with morphea-like skin changes occurring at the injection sites. Currently, the treatment plan includes potent topical steroids combined with topical calcitriol and the initiation of systemic methotrexate therapy.

DISCUSSION

Morphea is an inflammatory disorder characterized by fibrosis of the skin resulting in thickening of the dermis and subcutaneous tissue, which may extend to deeper underlying structures like fascia, muscle, and bone. Morphea differs from systemic sclerosis in that it does not involve internal organs, Raynaud's phenomenon, nailfold capillary changes, or sclerodactyly.[3] The pathogenesis is not clear but likely is multifactorial. The currently accepted proposed mechanism involves genetic factors and environmental exposures resulting in small vessel

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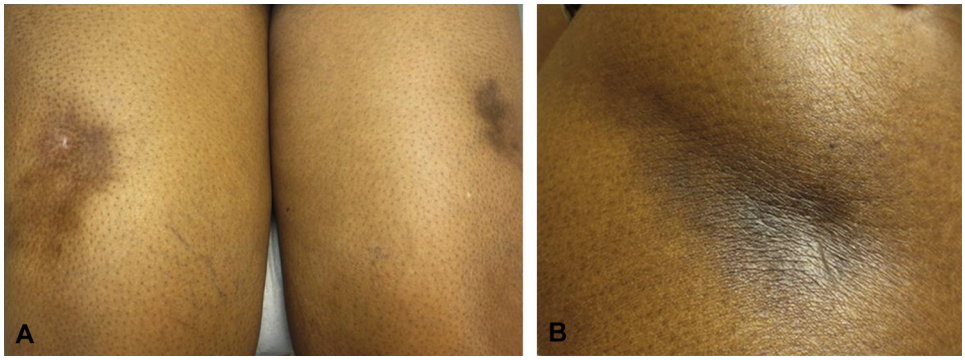

Fig 1. Depressed, indurated, bound-down hyperpigmented plaques involving anterior thighs (**A**) and right hip (**B**).

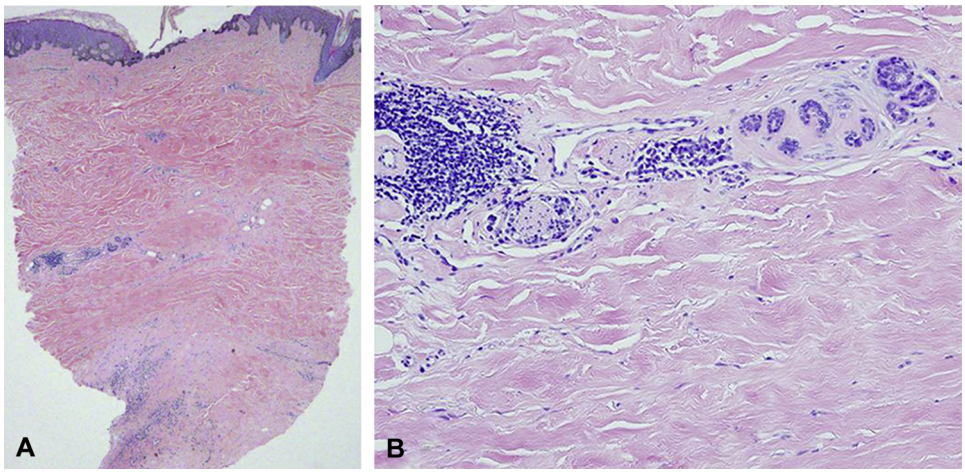

Fig 2. **A**, Punch biopsy from the right thigh shows thickened collagen bundles extending into the subcutaneous fat, paucity of adnexal structures, and a deep reticular lymphocytic infiltrate (Hematoxylin-eosin stain; original magnification: ×4). **B**, Higher magnification image shows thickened collagen, lymphoplasmacytic infiltrate, and entrapment of the eccrine glands by collagen (original magnification: ×20).

damage and the release of profibrotic cytokines. These factors lead to a disruption in the balance of collagen production and destruction.[3] Vascular injury is believed to be the initial step leading to increased expression of adhesion molecules, recruitment of inflammatory cells, and an increase in the production of profibrotic cytokines (transforming growth factor beta), which promotes production and decreases destruction of collagen.[4] Numerous exogenous factors have been reported to play a role in the development of morphea, including trauma, injection, vaccination, infections, and radiation therapy.[3,5]

Recently, there have been reports of sclerosing skin disorder development secondary to various biologic agents, including tumor necrosis factor inhibitors and IFN-β.[2,6] More recently, IFN-β1a was reported to possibly trigger systemic sclerosis in patients with multiple scleroris.[2] The proposed mechanism involves an IFN-induced activation of fibroblasts via T helper 2 (Th2) cytokines.[2] Autoreactive T cells are thought to play an important role in MS and systemic sclerosis (SSc), and antigen-driven Th2 cell activation and upregulation of interleukin 4 (IL-4) have been identified in active SSc.[7] This cytokine profile is also characteristic in MS patients after initiating IFN-β treatment.[8] Therefore, skin sclerosis may develop subsequent to an IFN-mediated Th2 upregulation.[9]

Our patient had cutaneous changes clinically and histologically consistent with morphea at the injection sites a few months after initiation of IFN-β1a therapy. Although pain, inflammation, and induration at injection sites are not uncommon, other, less common reactions, such as panniculitis, lipoatrophy, skin necrosis, ulceration, cutaneous vasculitis, lupus erythematosus–like lesions, and SSc have been reported.[10] Our patient presented only with localized

sclerodermalike changes confined to the injection sites and no other signs suggestive of limited or diffuse systemic sclerosis. Hugle et al[2] reported the occurrence of sclerosing skin disorders in 12 patients treated with IFN, of which, 8 had limited cutaneous systemic sclerosis, 3 had diffuse cutaneous SSc, and 1 had antisynthetase syndrome. Eleven of these patients had Raynaud's phenomenon and none had morphea.[2] With regard to patients injecting biologic therapies, it is difficult to determine if this cascade of events is caused by either vascular damage at injection sites or a treatment-induced alteration in the cytokine profile. The clinical improvement of our patient and reversibility of lesions in previously reported cases[6] on cessation of biologic therapy supports the latter rather than the former. An initial approach to the management would include discontinuation of IFN therapy, the addition of topical steroids or tacrolimus, ultraviolet phototherapy, or, depending on the severity of the disease, the addition of methotrexate with or without systemic steroids or other immunosuppressive therapies.

The development of morphealike skin changes at the sites of IFN injections in our patient could be related to dysregulation of the Th1/Th2 cytokine balance within the local microenvironment or secondary to trauma or a combination of both. Whereas the development of morphea secondary to trauma has been well appreciated, morphealike skin changes occurring at the sites of IFN-β injections have not been reported to the best of our knowledge. It is possible that this adverse event is underreported, as biopsies in such cases are frequently not performed.[10]

We report on a patient with MS who had woody induration clinically and histologically consistent with morphea at the sites of subcutaneous IFN-β1a injections. The increasing use of biologic agents to treat chronic medical conditions and the potential interplay between these therapies and patients' cytokine profiles necessitates awareness of all possible cutaneous side effects.

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