Deep morphea induced by interferon-β1b injection

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INTRODUCTION

Morphea, also known as *localized scleroderma*, is an uncommon fibrosing condition of the skin and underlying tissue. Although the etiology is unknown, morphea is considered an autoimmune condition in which genetic and environmental factors contribute to disease onset.[1] Although most cases are spontaneous, several inciting factors are associated with morphea, including trauma, surgery, radiotherapy, and infections.[2,3] Morphea has also apparently been triggered by injections such as vaccination, vitamin B12, and vitamin K.[3] However, morphea after interferon-β1b (IFN-β1b) injection is rarely reported. Injection site reactions (ISR) to IFN-β1b range from mild erythema to ulceration,[4] and a case of deep morphea after IFN-β1b injection is described here.

Abbreviations used:

IFN: interferon
ISR: injection site reaction
MS: multiple sclerosis

CASE REPORT

A 60-year-old white man with multiple sclerosis (MS) was receiving IFN-β1b (Betaseron) injections, 0.25 mg every 2 days subcutaneously for 5 years. He rotated injection sites from the thighs to the abdomen and frequently reported mild ISRs that were self-limiting. However, in March 2014 he noted severe redness, swelling, and pain on the right inner thigh at an injection site. He was otherwise well and afebrile but his condition was assessed in the hospital as possible cellulitis and he was started on intravenous antibiotics. Deep vein thrombosis was excluded by Doppler ultrasound studies. He had no prior history of connective tissue disease or Raynaud's phenomenon, and his other medication included aspirin, bupropion, and venlafaxine. He stopped receiving IFN-β1b injections on the right thigh, but the lesion continued to expand. Despite a 2-week antibiotic course, there was no improvement, and he was referred to the dermatology department to rule out a noninfectious etiology.

Examination found a well-looking man with Fitzpatrick type II skin. The entire right lower limb was edematous, with a tender demarcated area of intense erythema, induration, and peau d'orange on the medial thigh (Fig 1, *A*). Panniculitis was suspected, and the lesion was biopsied with a deep ellipse. Histopathology results showed a normal epidermis with increased collagen bundles in the dermis extending to the subcutis and a squared-off appearance to the dermal-subcutis junction. There was decreased adipose tissue surrounding adnexal structures. In a perivascular and periadnexal location, there was a lymphocytic infiltrate containing occasional eosinophils and rare plasma cells (Fig 2). Complete blood count showed a mild peripheral eosinophilia, and the antinuclear antibody screen result was negative. The final clinical diagnosis was, therefore, deep morphea (morphea profunda subtype), and it was postulated that the IFN-β1b injection could have played a role.

Because of the severity of the symptoms, the patient was treated with oral prednisone, 20 mg/d, together with methotrexate, 10 mg/wk. IFN-β1b injections were discontinued, and his MS remained stable. There was a slow improvement in the lesion on the right thigh. One month later, a similar

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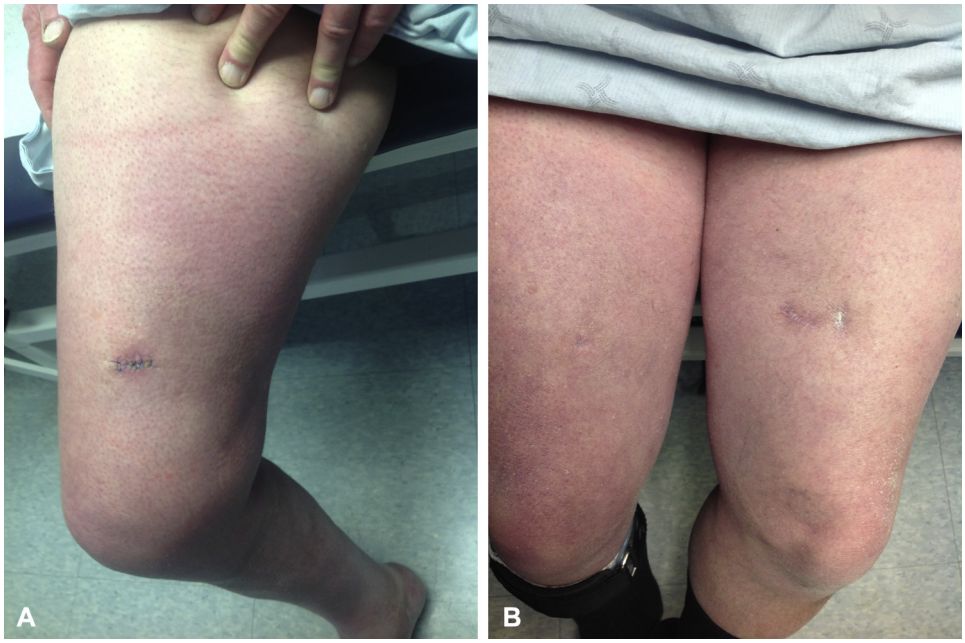

Fig 1. A, Morphea profunda: an erythematous, ill-defined plaque at the site of IFN-β1b injection on the right anterior thigh. Biopsy site shown. **B**, Follow-up: decreased erythema and induration of plaques on both thighs after treatment with prednisone and methotrexate for 8 months. The small superficial scar on the right thigh was from the biopsy, and the scar on the left thigh was from incision and drainage.

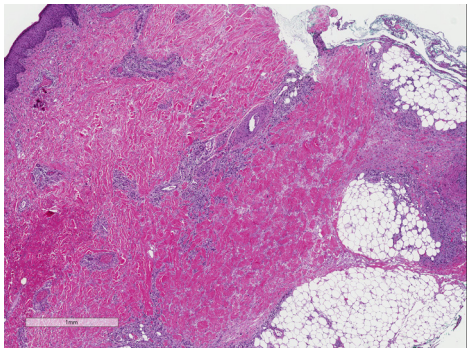

Fig 2. Normal epidermis with dermal sclerosis extending to subcutis. Perivascular and periadnexal lymphocytic infiltrate with eosinophils. Reduced periadnexal fat. (Hematoxylin-eosin stain; original magnification: ×40.)

indurated plaque developed on the left thigh at a site of former injections, which formed an abscess requiring incision and drainage. Culture found *Staphylococcus aureus,* and he was treated with oral cephalexin for 10 days. When the infection resolved, the dose of prednisone was increased to 50 mg/d, and the methotrexate dose was increased to 15 mg/wk. Over the next 6 months, there was gradual improvement in both thigh lesions, and the treatment was tapered. He did not have similar indurated lesions on the abdomen. At follow-up 8 months after his initial visit, there was a near-complete remission with superficial sclerosis and mild lipoatrophy on the left thigh and a small superficial scar on the right thigh (Fig 1, *B*).

DISCUSSION

Morphea, also known as *localized scleroderma*, is a fibrosing disorder of the skin and subcutaneous tissue.[2] It is distinguished from systemic scleroderma by the lack of internal organ involvement. Morphea can be classified into plaque, linear, generalized, bullous, and deep subtypes based on clinical features.[5] Deep morphea encompasses morphea profunda, subcutaneous morphea, and disabling pansclerotic morphea. Eosinophilic fasciitis has also been considered a variant of deep morphea.[5] The underlying etiology of morphea remains elusive. The condition is associated with autoimmune thyroid disease as well as alopecia areata, vitiligo, lichen planus, and type I diabetes.[1,3]

The following diagnostic criteria have been proposed for morphea profunda: (1) clinical—diffuse, taut, bound-down, deep sclerosis of the skin; (2) histopathologic—appreciable hyalinization and thickening of collagen bundles of both the panniculus and the fascia with a dense inflammatory cell infiltrate; (3) therapeutic—response to antimalarial agents, systemic corticosteroids, or other anti-

inflammatory agents. In addition, patients with deep morphea can show peripheral eosinophilia.[5]

Several triggers for morphea have been reported, including surgery, penetrating trauma, injection, zoster, radiation therapy, diagnostic x-ray, and extreme exercise.[2,3,6] A recent study highlighted the role of skin trauma in morphea in both adults and children.[6] In terms of injections, rare cases of morphea after vitamin B12 and vitamin K injections and vaccinations have been reported.[3] One case of a morpheaform reaction to IFN-β1b injection on the thighs and abdomen was reported in 2013, and this patient, as in this reported patient, was also using the agent for a long time before the onset of symptoms.[7] A case of morphea on the anterior thighs 6 months after injection of IFN- β1a was recently reported; lesions appear to be similar to this case.[8] Whether the sclerosing reaction in these cases is caused by physical trauma from repeated injection or by a profibrotic effect from interferon itself remains controversial. Cytokine dysregulation has been implicated in the pathogenesis of systemic sclerosis, with tumor necrosis factor, T helper 2 cells, and interleukin-4 playing a role in activating fibroblasts[9,10]; a similar mechanism may be at play in certain cases of morphea.

Interferon beta is an effective therapy for relapsing-remitting MS, but one of the common side effects is ISR, which occurs in up to 85% of patients. These reactions vary widely from mild erythema and edema to indurated plaques and ulcers.[4] Areas with less subcutaneous fat, such as the thighs, are more frequently affected by ISR. Cases of lupus panniculitis, and lobular panniculitis, have been described.[11,12]

Treatment of morphea can be challenging, but many cases involute spontaneously and mild cases can be followed. There can, however, be severe atrophy or scarring as possible sequelae. Widespread, linear, or deep morphea is increasingly managed with systemic agents like prednisone or methotrexate, and phototherapy with ultraviolet A1 has also been used effectively.[2]

This case illustrates the potential for severe ISR from IFN-β1b and also emphasizes the role of trauma or cytokine dysregulation in the pathogenesis of morphea and the utility of immunosuppressive therapy for deep morphea.

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