Lipoatrophy Associated With Glatiramer Acetate Injections for the Treatment of Multiple Sclerosis

Linda Hwang, MD, Houston, Texas
Ida Orengo, MD, Houston, Texas

We present a 35-year-old woman with symmetrical lipoatrophy induced by daily glatiramer acetate injections. Glatiramer is indicated as an effective treatment for relapsing-remitting multiple sclerosis (MS). This adverse effect has not been widely reported in the literature; to our knowledge, this is only the seventh reported case of this phenomenon. We suspect that more cases will be identified in the future as glatiramer injections become increasingly prescribed for patients with MS.

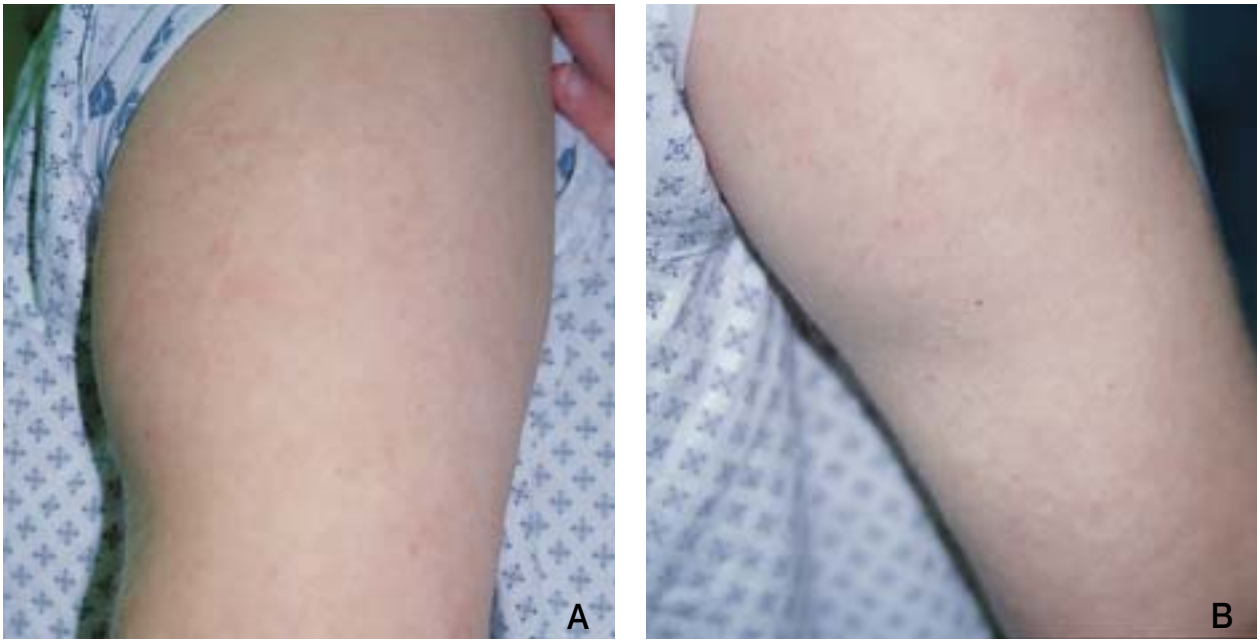
Case Report

A 35-year-old white woman presented with a 1-year history of progressive asymptomatic indentations over various sites of her body. Her medical history revealed that she had had relapsing-remitting multiple sclerosis (MS) for 7 years and that she had been treated with daily glatiramer injections for 2 years. The patient denied constitutional symptoms, trauma, or other skin problems, and she was not taking any other medications at the time. Physical examination revealed symmetrical soft tissue depressions periumbilically and over the anterior thighs, posterior upper arms, and lateral hips. There was no associated erythema, warmth, tenderness, or induration (Figure), and the affected areas corresponded exactly to the sites of injection. This markedly symmetrical soft tissue atrophy was consistent with lipoatrophy attributable to glatiramer injections. To our knowledge, only one case of this unusual adverse reaction (which documents a handful of occurrences) has been reported.[1]

Drs. Hwang and Orengo are from the Department of Dermatology, Baylor College of Medicine, Houston, Texas. Reprints: Ida Orengo, MD, Department of Dermatology, Baylor College of Medicine, One Baylor Plaza, FB800, Houston, TX 77030.

Glatiramer is a synthetic polymer of L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. Glatiramer's exact mechanism of action is unknown, but it is speculated that it alters T-cell immune function by inducing antigen-specific T-suppressor cells, interfering with class II major histocompatibility complex antigen binding,[2] and modifying cytokine profiles.[3] Glatiramer has been shown to reduce the incidence and severity of experimental allergic encephalomyelitis, an animal model of MS. Clinical trials also have demonstrated that treatment of relapsing-remitting MS with glatiramer injections results in fewer recurrences.[4] However, the systemic effects of the drug on the immune system have not been identified. The commercially available form is a white, sterile, lyophilized powder containing 20 mg of glatiramer acetate and 40 mg of mannitol supplied in refrigerated single-use vials for subcutaneous administration after reconstitution with sterile water.[5] The patient must inject the mix subcutaneously at various recommended sites on the body and should not use any site more than once each week. After each injection, the patient is instructed to press a cotton ball on the injection site for a few seconds without massaging.

Our patient reportedly followed the drug instructions conscientiously. In addition, she often placed icepacks on the sites to relieve postinjection pain and pruritus, which usually lasted 30 to 45 minutes. Occasional episodes of postinjection swelling also were noted and generally resolved after a day. The only other adverse effects were weight gain, mild anxiety and confusion, and occasional vertigo. She denied flulike symptoms, peripheral edema, headaches, palpitations, chest pain, gastrointestinal symptoms, tremor, weakness, speech problems, dyspnea, and ear or eye problems, all of which have been reported rarely in multi-



Upper arm with lipoatrophy at injection site (A and B).

center controlled trials.[4] At follow-up, the patient was highly motivated and chose to remain on the medication.

Comment

In phase 3 clinical trials with a 2-year follow-up (N=125), glatiramer was found to have a good safety profile.[4] Data from 201 patients receiving glatiramer injections in placebo-controlled trials showed that injection-site reactions, vasodilatation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety, and hypertonia were the most common significant adverse effects.[4] Of the injection-site reactions, erythema was seen in 66% of the patients, inflammation in 49%, pain in 73%, and pruritus in 40%. Soft tissue atrophy was not reported.[5]

Lipoatrophy due to injection has been described in conjunction with several other drugs, most commonly insulin, but also antibiotics and steroids. Localized lipoatrophy also has been reported as a result of acupuncture.[6] Although the pathophysiology of this phenomenon is still unexplained, theories include trauma-induced release of macrophage cytokines such as tumor necrosis factor and interleukin 1, both of which have been reported to enhance lipocyte catabolism in vivo. Another possibility is direct trauma induced by refrigerated solutions of both insulin and glatiramer. In addition, it may be possible that immune reactions to the injected drug, such as those seen in less-purified forms of insulin, may further contribute to the incidence of lipoatrophy. In the case of glatiramer, an immune modulator, a local immune injection reaction may be a factor.

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