

Dermographism: An Adverse Effect of Atorvastatin

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Dermographism, or skin writing, is the most common type of physical urticaria,¹⁻⁴ manifesting as pruritic linear wheals and erythema secondary to minor trauma, such as rubbing or stroking the skin. This reaction in the superficial dermis occurs within seconds to minutes after mechanical irritation and typically resolves within 1 to 2 hours. Usually there are no associated systemic signs and symptoms. Precipitating factors can include viral infections, antibiotics, and emotional distress. In most cases, however, the cause is unknown.⁵

Atorvastatin (Lipitor) is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor commonly used in treatment of hypercholesterolemia. Atorvastatin and other HMG-CoA reductase inhibitors have been well tolerated with similar adverse effect profiles.⁶ Less than 2% of 2,502 patients in a postmarketing atorvastatin study withdrew from the study because of adverse effects.^{7,8} The most common adverse effects include gastrointestinal disturbances, such as dyspepsia, abdominal pain, constipation, and flatulence. More serious adverse effects are liver insufficiency and myopathy.⁸

Cutaneous adverse reactions secondary to HMG-CoA reductase inhibitors are infrequent, which might be explained by extensive first-pass metabolism in the liver resulting in low serum concentrations.⁹ HMG-CoA reductase inhibitors have been implicated with eczematous rashes,^{9,10} lichenoid eruptions,¹¹ cheilitis,¹² and ichthyosis-like reactions.¹³ These reactions have been explained by decreased epidermal cholesterol synthesis leading to impairment of the cutaneous barrier function. In addition, HMG-CoA reductase inhibitors have

been associated with toxic epidermal necrolysis,¹⁴ urticaria, angioedema, photosensitivity, and radiation recall.¹³ To our knowledge, this case is the first reported of dermographism thought to be related to any HMG-CoA reductase inhibitor. Inhibition of epidermal cholesterol synthesis does not appear to explain dermographism.

Case Report

A 40-year-old woman came to her physician in mid-June with a 4-month history of urticaria. Her medical history was notable for well-controlled type 1 diabetes mellitus, hypercholesterolemia, hypothyroidism, alopecia totalis, and a childhood history of a penicillin-induced rash. She had no medical history or family history of urticaria or atopy. She was compliant with medications, which included norethindrone acetate/ethinyl estradiol 1/20 for 21 years, NPH insulin for 20 years, and insulin lispro for 1 year. She had taken levothyroxine for 13 years; however, the dose had been increased from 175 μg to 200 μg 5 months earlier. Atorvastatin 10 mg daily was also begun at this time. She used no vitamins or herbal medicines.

One month after atorvastatin was started, the patient reported mild itching with red, linear papules appearing within seconds to minutes after application of light pressure to the skin. The urticaria resolved spontaneously within 1 hour. She initially thought the urticaria resulted from contact with yellow pollen on her Labrador retriever's paws. This theory was discounted after the pollen season ended and her urticaria continued. She then noticed a similar response after carrying books or shopping bags over her arms for a short distance. She drew a "happy face" on her forearm, and, as expected, urticaria developed immediately and then faded within an hour. The same "happy face" reappeared the next day when she became overheated.

There had been only mild irritation on localized areas of her body without interfering with usual

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activities until the day before her visit to her physician's office. At this time, she reported diffuse urticaria associated with nausea, vomiting, abdominal cramping, and diarrhea. She self-medicated with diphenhydramine, which alleviated the symptoms. Findings during the initial skin examination were unremarkable, as the rash had resolved. Dermographism was confirmed when a line was drawn on her ventral forearm with an ink pen.

The patient denied emotional distress, ingestion of uncommon foods, or use of new soaps, lotions, or washing powders. Based on the temporal relation, atorvastatin was presumed to be the most likely cause and was discontinued. The following day, the patient developed diffuse urticaria with gastrointestinal distress and new-onset left wrist pain with edema and tenderness of her soles. She again self-medicated with diphenhydramine and fexofenadine for symptomatic relief. Involvement of the deep dermis and subcutaneous tissue of her nonpruritic soles was consistent with angioedema. Erythema multiforme with classic target lesions was noted on her lower trunk and thighs. Within 2 to 3 days, angioedema and erythema multiforme had resolved. Cetirizine and nizatidine were prescribed to be taken routinely for 1 week and then as needed for an additional week. Episodes of dermographism became less frequent with complete resolution within 3 months. There have been no further episodes within the last 6 months. She was not rechallenged with atorvastatin or other HMG-CoA reductase inhibitors because it not known whether a similar response would occur. She is currently attempting to manage her hypercholesterolemia with diet alone.

Discussion

Urticaria is a common condition diagnosed by family physicians. Referrals or consultations are usually not needed, except perhaps for confirmation or hypersensitivity testing. Dermographism, a type of urticaria, occurs in 25% to 50% of the normal population, yet only 5% of patients are highly symptomatic.¹⁵ Coexistence or clustering of different types of urticaria in a patient is common.^{2,4,16}

Evaluation of patients with urticaria should include a detailed history of the onset and duration of both cutaneous and systemic manifestations. A thorough skin examination, noting size, thickness,

and distribution of lesions, is imperative. A thorough history should also be obtained concerning prescription and over-the-counter medications, uncommon foods, recent travel, and such environmental exposures as pollens and chemicals. Clinical diagnosis of dermographism can be confirmed by development of linear wheals induced by firmly stroking the skin with the edge of an object. This reaction occurs immediately and usually resolves within 1 hour. Total resolution of dermographism usually occurs within months to years, with severe cases lasting as long as 10 years.⁴ Differential diagnosis of dermographism can include contact dermatitis and delayed-pressure urticaria, the latter exhibited by nonpruritic, painful wheals occurring 6 to 8 hours after pressure, relieved with corticosteroids, and resolving within 8 to 24 hours.¹⁷

The clinical picture of our patient supports a diagnosis of dermographism. The patient had symptomatic dermographism with coexisting angioedema and erythema multiforme. Dermographism was confirmed when her arm was stroked with an ink pen. The patient denied new contacts and complained of pruritic, painless lesions, which became evident minutes after exposure and were relieved with antihistamines. Episodes of dermographism completely resolved within 3 months after atorvastatin was discontinued.

Initial treatment of dermographism should include cessation of any suspected agents. Atorvastatin was determined to be the most probable cause in our patient and was discontinued. If the cause is unknown, discontinuation of all suspected drugs is wise. Environmental changes should also be considered. Treatment might be unnecessary unless the patient is highly sensitive and continues to react with even the slightest trauma. For these patients, antihistamines help by inhibiting histamine-mediated vasodilation and vessel fluid loss. Hydroxyzine, an H₁ antihistamine, has been cited as the drug of choice for symptomatic dermographism.^{4,5} The effectiveness of nonsedating antihistamines and hydroxyzine specifically for chronic idiopathic urticaria is, however, comparable.¹⁸⁻²⁰ The use of a combination of H₁ and H₂ antihistamines for dermographism is controversial.⁵

Because there have been no other reports of dermographism secondary to HMG-CoA reductase inhibitors, we can only speculate on possible mechanisms. The impaired barrier dysfunction responsible for eczematous-type reactions does not

seem to explain urticaria as seen in this case. Urticaria occurs when cutaneous mast cells become activated and release vasoactive mediators. In dermographism, histamine is likely the primary mediator, as antihistamines are effective in treatment. Contributions of other mast cell mediators, such as prostaglandins, leukotrienes, platelet-activating factor, serotonin, and chemotactic factors for eosinophils and neutrophils, are not as clearly defined.²¹

Mast cell activation can also occur indirectly secondary to an immunoglobulin E (IgE)-directed mediator release.^{16,22,23} Kaplan reported acute urticaria is often allergic where IgE is directed to an exogenous antigen, such as a food or drug.²¹ Many allergic reactions occur after sensitization from a previous exposure or with prolonged administration.²⁴ This delayed response might explain why urticaria did not develop until 1 month after atorvastatin was initiated in our patient. A similar delay has been shown with penicillin reactions requiring 10 to 20 days for development of penicillin-specific IgE.²³ IgE involvement could be also be supported by recurrence of the "happy face" on the following day, which suggests immunologic memory. Auto-immune mechanisms can also activate mast cells to release histamine. This patient had diabetes, hypothyroidism, and alopecia totalis, all considered autoimmune diseases. Autoimmunity might therefore have partially contributed to dermographism. Because dermographism resolved after atorvastatin discontinuation, however, autoimmunity was not considered the sole cause.

As discussed, this case of dermographism secondary to atorvastatin therapy is a presumptive diagnosis. There was no histologic examination and no rechallenging, as the latter should not be done after development of such high-risk reactions as urticaria, vasculitis, and erythema multiforme major.¹³ There was a temporal relation, however, as dermographism occurred approximately 1 month after atorvastatin was begun and became less frequent and subsequently resolved after the drug was discontinued. Because there have been no other case reports of dermographism secondary to HMG-CoA reductase inhibitors, a direct pharmacologic relation is unknown. Because these agents are so frequently prescribed, however, family physicians should be aware of the possibility of dermographism with atorvastatin.

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