Lamivudine (3TC)-Induced Contact Dermatitis

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The nucleoside analogue lamivudine (3TC) is commonly used in multidrug therapy of human immunodeficiency virus-1 disease because it not only potentiates the antiviral effects of other reverse transcriptase inhibitors, but it is also relatively nontoxic. We present a patient who developed a contact dermatitis to lamivudine after prolonged exposure.

Lamivudine (3TC) is the negative *cis* enantiomer of 2'-deoxy-3'-thiacytidine. It is a synthetic cytidine 2',3'-dideoxynucleoside analogue with the unnatural 2R,5S absolute configuration. Lamivudine belongs to the nucleoside analogue group of antiretroviral drugs that includes zidovudine, didanosine, zalcitabine, and stavudine.[1]

Lamivudine passively diffuses across cell membranes, after which it is phosphorylated to its putative active metabolite, lamivudine-5'-triphosphate. Lamivudine triphosphate then inhibits viral reverse transcriptase by competing with 2'-deoxycytidine-5'-triphosphate, and results in human immunodeficiency virus (HIV) DNA chain termination because it lacks the 3'-hydroxyl group.

This drug has a unique resistance profile, and has the ability to delay resistance to zidovudine and restore zidovudine sensitivity in zidovudine-experienced patients. Lamivudine is widely used in multidrug combination therapies, which at present usually include HIV-1 protease inhibitors. These multidrug combinations are used to potentiate the antiviral response and to delay the development of resistance.

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Lamivudine is well tolerated either alone or in multidrug therapy. Gastrointestinal side effects are the most common. Although pancreatitis has been reported in children receiving multidrug therapy that includes lamivudine, the pancreatitis has not been proven to be directly related to lamivudine. We report what we believe is the first case of allergic contact dermatitis to lamivudine.

Case Report

A 40-year-old white woman, a health care provider, was given triple HIV drug therapy after contact with blood products from an HIV-positive patient. Approximately 1 week after starting the medication, the patient had capsules of zidovudine, indinavir, and a tablet of lamivudine in her hand to take, when she was stopped. The patient proceeded to hold the medication during a prolonged conversation lasting more than 30 minutes.

Approximately 2 to 3 days later, the patient noticed an eruption with pruritus extending from the palm down the forearm. The eruption worsened over the next few days (Figure 1).

A biopsy from the involved wrist showed an intraepidermal vesicular dermatitis with a mixed inflammatory infiltrate containing mononuclear cells as well as neutrophils and eosinophils (Figure 2). The patient was given potent topical steroids with resolution of the eruption.

The patient continued the anti-HIV medications for approximately 2 more weeks with no systemic reactions. However, she did stop the treatment early because she had problems complying with the schedule for taking the medication.

Three months following clearing of the eruptions, the patient was patch tested on the back using powder from the capsules of zidovudine and indinavir, broken-up capsules from zidovudine and indinavir, and a crushed lamivudine tablet. These materials were mixed in petrolatum in an approximately 1/4 dilution. The petrolatum mixtures were placed in Finn

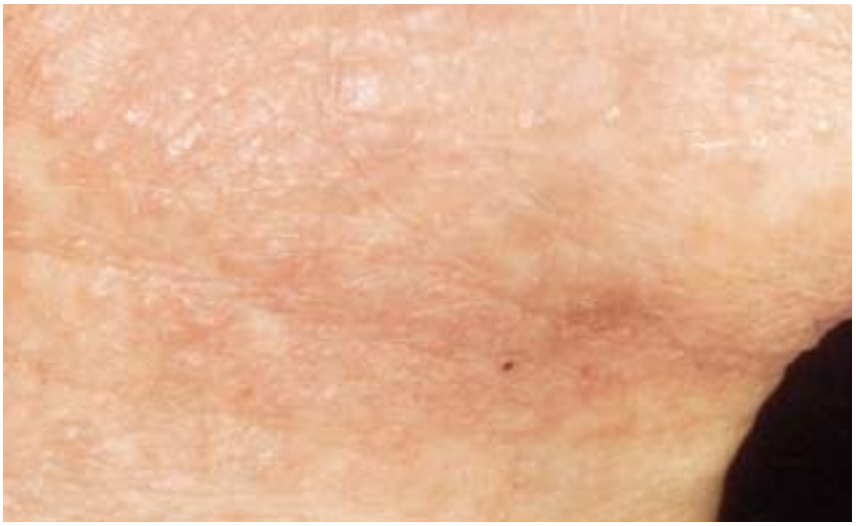

FIGURE 1. Erythematous vesicular eruptions over the lower palm and extending down the wrist.

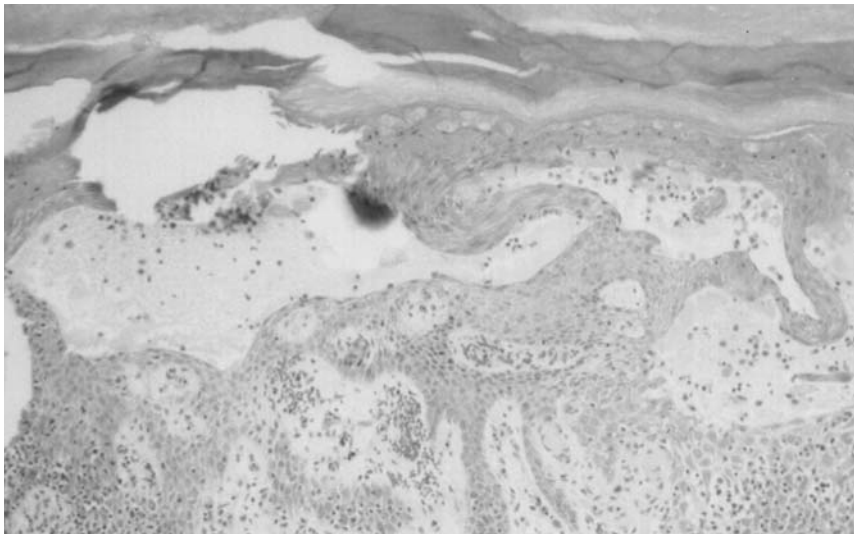

FIGURE 2. Intraepidermal spongiosis with intraepidermal blister formation. There is a mixed inflammatory infiltrate containing mononuclear cells as well as neutrophils and eosinophils (H&E; original magnification, X 100).

chambers on scanpor tape. These chambers were then placed on the patient's back. The patient returned at 48 hours after application of the Finn chambers. The Finn chambers were removed, and the first readings were performed approximately 1 hour later. At that time, the patient had a +2 reaction at the lamivudine site. The patient returned for a second reading at 96 hours after application, and a +3 reaction was present at the lamivudine site.

Comments

Repeated attempts were made to obtain the inactive ingredients contained within the lamivudine tablet (magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and opaddy YS-1-7706-G white dye) from the manufacturer; however, these attempts were unsuccessful. All the inactive ingredients except for the dye were contained in the zidovudine powder, and patch testing was negative with zidovudine powder. There have been no reports of any cutaneous eruptions or reactions to opaddy YS-1-7706-G white dye.

Lamivudine has good systemic bioavailability. It is not significantly metabolized and is eliminated largely unchanged via the kidneys.[1,2] In addition, lamivudine causes minimal inhibition of mammalian DNA polymerase and does not disrupt mitochondrial DNA synthesis. These properties probably explain lamivudine's lack of cytotoxicity in established hemopoietic cell lines, and the absence of peripheral neuropathy, a side effect that does occur with other nucleoside analogues.

Lamivudine does not need facilitation to pass through membranes, and is secreted mainly unchanged.[1,2] Lamivudine is not highly reactive and does not appear to react with extracellular proteins. Thus, there is a low probability that it would be processed through the exogenous system for presentation with HLA class II antigens. Other molecules that easily pass through membranes, as does lamivudine, may in-

duce contact dermatitis through the endogenous system, to be presented with HLA class I antigens.[3] However, not only are these molecules lipophilic, low molecular weight compounds, but they are also reactive compounds, and, again, the low innate reactivity of lamivudine would make conventional endogenous presentation unlikely.[4,5]

Although single nucleotides and nucleotide analogues are not used to induce immunologic responses, mycobacterial DNA and other nonprotein molecules are known to induce T cell-specific reactions. The antigenicity of bacillus Calmette-Guérin and other bacterial DNA appears to be related to differences in nucleotides including nucleotide side chains.[3,4] Some of these immune stimulatory oligonucleotides induce, and are used to induce, interferon-γ and interleukin-12; Th-1 cytokines present in allergic contact dermatitis.[6] In addition, the presentation of nonprotein molecules may be more diverse than is presently characterized. The presentation through more than one subtype of CD1-restricted T cell populations appears to occur in the development of immunologic reactions to an ever-more diffuse spectrum of nonprotein molecules.[7] Thus, CD1-restricted T cell populations of cells or other nonconventional antigen-presenting cells may play a role in our patient's reaction to lamivudine as well as cutaneous contact dermatitis to other molecules.[7]

Lamivudine is a valuable part of the multidrug therapy now being used in a significant percentage of HIV-1-positive patients. Induction of contact dermatitis appears to be one of the relatively rare side effects of this medication and may not predict systemic reactions.

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