Methotrexate Sodium–Associated UV Reactivation in a Patient With Acute Lymphoblastic Leukemia

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UV reactivation is an uncommon reaction characterized by recurrent inflammation in areas of prior sunburn or UV exposure following the administration of a triggering drug. We report a case of UV reactivation following administration of intravenous methotrexate sodium (MTX) 4 days after prolonged sun exposure in a 9-year-old boy with relapsed acute lymphoblastic leukemia. Our patient's MTX-associated UV reactivation occurred despite the use of sunscreen and without prior sunburn or sun-induced erythema, which suggests that even subclinical sun damage can trigger MTX-associated UV reactivation. Therefore, patients must be strongly encouraged to utilize a 3-pronged approach to sun safety including sun avoidance, sun-protective clothing, and broad-spectrum sunscreen use, especially during the week before MTX therapy.

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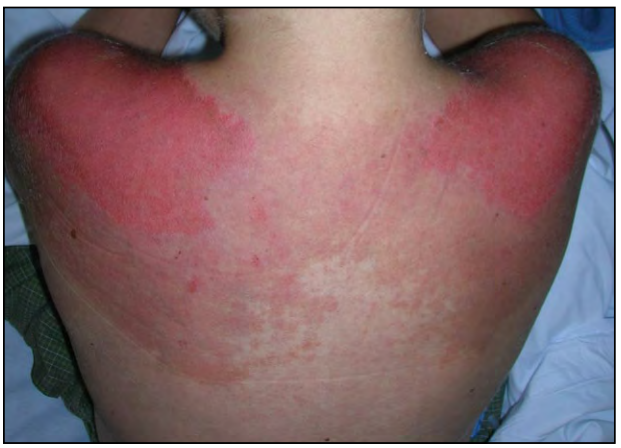
Case Report

A 9-year-old boy with relapsed acute lymphoblastic leukemia was admitted to the hospital for his first infusion of methotrexate sodium (MTX). Two days prior to admission, the patient reported spending the whole day at the pool and regularly applying sun protection factor (SPF) 50 sunscreen over his entire body. He reported no erythema or pain anytime prior to the MTX infusion. Six hours following the infusion, the patient began to experience burning, pain, and erythema over his shoulders, chest, and back. Over the next 2 days, he developed an erythematous macular rash with erosions over his shoulders (Figure), chest, superior back, lateral aspect of his arms, scalp, and tips of the ears. He did not have a history of radiation therapy and was not exposed to the sun at anytime following his MTX infusion, thereby excluding radiation recall or a phototoxic reaction. His rash was treated with emollients and improved over the following week.

Comment

UV reactivation is an infrequently reported side effect of MTX or antibiotics. Goldfeder et al[1] suggested revising the current inconsistent nomenclature surrounding this entity (eg, sunburn recall, photorecall, photodermatitis reactivation, UV recall, UV enhancement) by dividing UV reactivation into UV enhancement and UV recall based on the time frame between sun exposure and drug therapy. They indicated that UV reactivation that occurs when the drug is administered within 1 week of UV exposure should be termed *UV enhancement*, and reactivation



Erythematous macular rash with erosions limited to the most sun-exposed skin of the shoulders and superior back.

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reactions that occur when the drug is administered months or years after UV damage should be termed *UV recall*. This terminology follows that used for reactions in areas of prior radiation therapy (eg, radiation enhancement, radiation recall).

This proposed nomenclature helps to simplify the inconsistent terminology surrounding UV reactivation. However, UV enhancement and UV recall differ in more than time frame and may represent separate pathophysiologic entities.[2] UV enhancement typically is associated with MTX use[1-3] and sunburn-type reactions, while UV recall usually is linked with antibiotic use and morbilliform or maculopapular lesions.[1,2] Furthermore, although the pathogenesis of either type of UV reactivation remains poorly understood, they may be dissimilar.[2]

The mechanism of MTX-associated UV reactivation may involve the antimitotic effects of MTX. UV light causes cellular damage, which stimulates basal cells in an attempt to repair them by increasing the synthesis of DNA, RNA, and proteins. By preventing this DNA/RNA proliferation through its antimitotic effects, MTX may increase the inflammation of the sunburn reaction.[4] However, because leucovorin rescue does not prevent MTX-associated UV reactivation,[5] this hypothesis is unlikely to explain the pathogenesis.[2] A second hypothesis for MTX-associated UV reactivation suggests that by inhibiting the local mononuclear response, MTX blocks one of the body's usual methods for controlling sunburn-induced inflammation.[4]

Antibiotic-associated UV reactivation (UV recall) is unlikely to occur by either mechanism because antibiotics are not antimitotic and sunburn-induced inflammation is completely resolved at the initial time of reaction.[2] To emphasize the difference between MTX-associated (UV enhancement) and antibiotic-induced (UV recall) UV reactivation, we will use the term *MTX-associated UV reactivation*.

Methotrexate-associated UV reactivation usually occurs within 1 to 5 days following a sunburn[1] and has never been reported to occur more than 8 days following UV exposure.[6] The lesions usually have a sunburnlike appearance and are more severe than the initial sun exposure reaction.[1-8] Furthermore, MTX-associated UV reactivation has been reported to spare chronically sun-exposed skin, which suggests that only acute UV damage predisposes individuals to MTX-associated UV reactivation.[6] The histopathology of MTX-associated UV reactivation remains poorly characterized in the literature. Therefore, it is unclear if a specific spectrum of UV light contributes to the reactivation phenomenon.

In our patient, the morphology, distribution, and timing of MTX and light exposure are consistent with MTX-associated UV reactivation. Lymphoreticular malignancies alone have not been reported to cause erythema with these qualities; therefore, it is likely that our patient experienced MTX-associated UV reactivation. Because this reaction occurred in our patient with the use of sunscreen and without prior sunburn or sun-induced erythema, this case suggests that even subclinical sun damage can propagate MTX-associated UV reactivation. It remains unclear whether the degree of prior sun damage correlates with the severity of the MTX-associated UV reactivation. One other case report documented MTX-associated UV reaction without a history of sun-induced erthyema.[9]

UVA light is subdivided into UVC (200–290 nm), UVB (290–320 nm), UVA2 (320–340 nm), and UVA1 (340–400 nm) spectrums. The specific spectrum of UV light that contributes to the MTX-associated UV reactivation phenomenon remains unknown. Therefore, we recommend that patients adhere to a strict 3-pronged sun-safety approach to provide broad-spectrum protection the week before MTX administration. First, sun avoidance, which is the most effective form of sun protection, must be encouraged. Patients should seek shade whenever possible and limit their time in the sun between the hours of 10 AM and 4 PM. Second, patients must be counseled to wear sun-protective clothing, such as a long-sleeved shirt and wide-brimmed hat.[10] Thicker garments with a close weave are more sun protective because they transmit less UV radiation.[11] Third, a generously applied, broad-spectrum, water-resistant sunscreen with an SPF of at least 30 must be used. The American Academy of Dermatology recommends that sunscreen should be reapplied every 2 hours and after sweating or swimming.[10] Sun protection factor is defined as the minimal erythema dose of sunscreen-protected skin over the minimal erythema dose of unprotected skin and is chiefly a measure of UVB protection. Currently approved sunscreen filters are listed in the Table. Recently, the US Food and Drug Administration has instituted an in vitro test based on the critical wavelength value of 370 nm as its standard for UVA protection. New labeling on sunscreen products starting in the summer of 2012 will show an SPF value to reflect UVB protection and the label will show "broad spectrum" to reflect UVA protection.[14] Inappropriate sunscreen application, such as insufficient quantity or infrequent application; UV filter photodegradation; and physical removal (ie, swimming, sweating) also contribute to decreased efficacy of sunscreen.

Conclusion

It is important that patients do not rely solely on sunscreen use for sun protection, especially the week before MTX therapy. Patients must be encouraged to

US Food and Drug Administration–Approved Sunscreen Filters[12-14]

UV Filter	Synonyms	UV Absorption Spectrum
Avobenzone	Butyl methoxydibenzoylmethane	UVA1
Cinoxate	2-Ethoxyethyl-p-methoxycinnamate	UVB
Dioxybenzone	Benzophenone-8	UVB, UVA2
Ecamsule	Terephthalylidene dicamphor sulfonic acid	UVB, UVA2
Ensulizole	2-Phenylbenzimidazole-5-sulfonic acid, phenylbenzimidazole sulfonic acid	UVB
Homosalate	Homomenthyl salicylate	UVB
Meradimate	2-Aminobenzoate, menthyl anthranilate	UVA2
Octinoxate	2-Ethylhexyl methoxycinnamate, octyl methoxycinnamate	UVB
Octisalate	Octyl salicylate	UVB
Octocrylene	2-Ethylhexyl-2-cyano-3,3 diphenylacrylate	UVB
Oxybenzone	Benzophenone-3	UVB, UVA2
p-Aminobenzoic acid	Para-aminobenzoic acid	UVB
Padimate O	Octyldimethyl para-aminobenzoic acid, 2-ethylhexyl 4-dimethylaminobenzoate	UVB
Sulisobenzone	Benzophenone-4	UVB, UVA2
Titanium dioxide		UVB, UVA2
Triethanolamine salicylate	Trolamine salicylate	UVB
Zinc oxide		UVB, UVA1, UVA2

utilize the 3-pronged approach to sun safety including sun avoidance, sun-protective clothing, and broad-spectrum sunscreen use.

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