

# Methotrexate and the Photodermatitis Reactivation Reaction: A Case Report and Review of the Literature

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*Methotrexate is an antimitotic and immunosuppressive agent used for the treatment of cancer, psoriasis, and rheumatologic disorders and for the termination of ectopic pregnancies. Physicians advising patients on the use of methotrexate need to be aware of its possible side effects, including photosensitivity. We present a patient who received methotrexate for the termination of an ectopic pregnancy and experienced a severe reactivation of her sunburn. The literature was reviewed on the types of photosensitivity and their relationship to methotrexate.*

**M**ethotrexate (MTX) is an antimitotic and immunosuppressive agent that terminates DNA synthesis by inhibiting the enzyme dihydrofolate reductase.<sup>1</sup> MTX is utilized by oncologists, rheumatologists, and dermatologists in the treatment of conditions such as cancer, psoriasis, and rheumatologic diseases. Recently, obstetricians and gynecologists have been administering MTX for the nonsurgical termination of ectopic pregnancies.<sup>2,3</sup> All physicians who prescribe MTX need to be aware of its possible side effects. The well-known side effects include hepatotoxicity, pulmonary fibrosis, myelosuppression, mucosal ulceration, nausea/vomiting, alopecia, and renal toxicity.<sup>1</sup> Reactivation of an inflammatory response induced by radiation is less well known.<sup>4</sup> We present a case of a severe sunburn reactivation reaction occurring in a patient who received



**FIGURE 1.** Upper torso and arms show well-demarcated areas of erythema and crusting on the sun-exposed skin. Note the sparing of skin protected from ultraviolet rays by bathing suit.

MTX for the termination of an ectopic pregnancy and a review of the literature.

## Case Report

A 40-year-old woman became pregnant after artificial insemination. On the 25th gestational day, she experienced abdominal discomfort and was subsequently

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diagnosed as having a tubal pregnancy. The patient underwent a laparoscopic salpingostomy with removal of the tubal pregnancy. Eight days after discharge from the hospital, the patient was noted to have a rising  $\beta$ -human chorionic gonadotropin (hCG) titer. The patient was diagnosed as having persistent trophoblastic tissue. The decision was made to treat the patient with intramuscular (IM) MTX. Two days prior to receiving her first IM dose of MTX, the patient sustained a mild sunburn consisting of erythema without pain on her upper back, chest, arms, and legs; these were areas not covered by her one-piece bathing suit. The patient subsequently received her first IM dose of MTX without complications. Two days later, she noticed burning and increased redness on her skin at sites where she had been sunburned 4 days previously. Before she received her second dose of MTX, her physician referred her for a dermatologic consultation.

The patient was diagnosed as having sustained a grade 1 or 2 erythema from a sunburn and was cleared to receive her second dose of MTX. Within a few hours after receiving her second dose, the patient noted increased redness, pain, and burning of her previously sunburned skin. During the next 5 days, the patient experienced severe pain, blisters, and sloughing of her inflamed skin. The patient was then seen by our dermatologic department for consultation.

The physical examination revealed erythema on the sun-exposed areas of her upper back, chest, arms, and legs. The involved skin was erythematous to violaceous with bullae, desquamation, and hemorrhagic crusting. The skin protected from the sun by her bathing suit was not involved (Figure 1).

### Comments

MTX is reported to cause a photosensitivity reaction, in 5% to 6% of patients.<sup>5,6</sup> However, the type of photosensitivity is poorly characterized. The different types of photosensitivity and their relationship to MTX are reviewed below.

Photoallergy is a photosensitivity reaction that results when ultraviolet (UV) light converts a nonallergenic substance into an allergenic hapten, resulting in a delayed-type hypersensitivity (DTH) reaction. As would be expected of a DTH reaction, the onset of the rash is approximately 10 days after UV exposure.<sup>7,8</sup> MTX has not been reported to cause this type of photosensitivity.

Phototoxicity is a photosensitivity reaction that usually occurs within 24 hours of UV exposure as a result of direct cell destruction. Ultraviolet light causes an alteration in a substance that then becomes directly toxic to cells.<sup>8</sup> It is unclear from the literature review whether MTX can cause this type of reaction.<sup>7,9</sup>

The photosensitivity reaction known as radiation recall is a reactivation of an inflammatory response on skin irradiated months or years previously.<sup>10</sup> MTX has been reported to induce this type of photosensitivity.<sup>11-14</sup> However, on further evaluation of the published reports, it appears that at least some of the patients received radiation therapy and MTX concomitantly and, therefore, this may represent a form of photodermatitis reactivation reaction instead of a true radiation recall reaction.

Photodermatitis reactivation or photoreactivation reaction is an idiosyncratic reaction<sup>9,15,16</sup> that requires an initial exposure to UV light or x-rays, with or without ensuing erythema, and administration of MTX 2 to 5 days after exposure. This results in increased inflammation, erythema, and blisters in the areas previously exposed to electromagnetic radiation.<sup>7</sup>

The reactivation of a UV-induced burn due to MTX was first observed by Vogler and colleagues<sup>17</sup> in 1965 and subsequently by others.<sup>4,18-21</sup> However, the major understanding about MTX photoreactivation came from Moller's work.<sup>18</sup> In 1969, he induced skin erythema in patients with psoriasis by irradiating them with a high-pressure mercury-arc lamp prior to the administration of MTX. Patients irradiated between 2 to 4 days before MTX administration experienced a flare of their erythema. However, the sites irradiated simultaneously or more than 4 days prior to MTX administration showed no reactivation of erythema. Moller also used an animal model<sup>22</sup> to demonstrate that UV reactivation occurred when MTX was given between 2 to 3 days after UV exposure. Based on these experiments, it was realized that MTX does not cause a true phototoxicity reaction because the true phototoxicity reaction occurs within 24 hours of UV exposure. This reactivation reaction also has been observed in psoriatic patients receiving UV phototherapy and MTX.<sup>16,23</sup> However, since it is an idiosyncratic reaction, most patients receiving MTX and therapeutic UV radiation do not experience this reaction.<sup>9,15</sup>

UVA,<sup>14,24</sup> UVB,<sup>25</sup> and, rarely, x-rays<sup>26,27</sup> can elicit this reactivation phenomenon. The literature is replete with names for this reactivation reaction and include photoreactivation,<sup>7</sup> reactivation of acute inflammation,<sup>18</sup> reactivation of radiodermatitis,<sup>12</sup> reactivation of radiation dermatitis,<sup>5</sup> radiation recall,<sup>13</sup> reactivation of phototoxicity,<sup>14</sup> sunburn reactivation,<sup>4</sup> and sunburn recall reaction.<sup>16</sup> However, because this reaction can be induced by UVA, UVB, or, rarely, by x-rays, we propose that this reaction should be called the photodermatitis reactivation reaction or photoreactivation reaction as was proposed by Yokel et al.<sup>7</sup> Other medications also have been reported to cause a similar reaction and include cyclophosphamide, vincristine, bleomycin,

doxorubicin, doxorubicin hydrochloride, dactinomycin (actinomycin D), 5-fluorouracil, hydroxyurea, and vinblastine.<sup>21,28</sup>

The pathogenesis of MTX-induced photodermatitis reactivation is not well understood and has been observed despite folinic acid rescue,<sup>29,30</sup> which has reduced the incidence of other manifestations of MTX toxicity.<sup>31</sup> UV light causes cellular DNA damage that results in increased prostaglandin and cytokine production, which leads to the erythema seen in sunburned skin.<sup>7</sup> One to 3 days after a sunburn, the basal cells in the epidermis increase their DNA, RNA, and protein synthesis.<sup>4,32</sup> It is presumed that MTX inhibits local mononuclear cell response and DNA synthesis of these hyperproliferative basal cells, causing a delay in healing and thereby increasing the inflammation of the sunburn reaction.<sup>4</sup> This is manifested by increased erythema, bullae, desquamation, and pain. This reactivation reaction differs from other types of photosensitivity reactions including phototoxicity, photoallergy, and radiation recall for several reasons.

Due to its unique nature, MTX-induced photodermatitis reactivation also has been designated a "false photosensitivity reaction."<sup>33</sup> It is different from phototoxicity because it does not occur within 24 hours of UV exposure. It differs<sup>10</sup> from radiation recall because the radiation recall reaction can occur any time after radiation and not necessarily between days 2 and 5. MTX-induced photodermatitis reactivation reaction is differentiated from photoallergy since it occurs between 2 to 5 days and rarely up to a maximum of 7 to 8 days<sup>23,28</sup> following UV exposure while photoallergy occurs approximately 10 days after UV exposure.

In summary, MTX-induced photodermatitis reactivation is a unique, idiosyncratic, and rare photosensitivity reaction that may occur if MTX is administered between 2 to 5 days following excessive exposure to UV light or, rarely, x-rays. It can result in significant erythema and blistering. It cannot be prevented by folinic acid rescue and does not occur if MTX is given simultaneously with UV radiation or if MTX is given more than 5 to 7 days after exposure to UV radiation. Because this reaction can be induced by UVA, UVB, or both (rarely x-rays), we propose that this reaction be called the photodermatitis reactivation reaction or photoreactivation reaction. Therefore, if a patient has a history of erythema induced by a sunburn or from therapeutic UV or radiation therapy in the preceding 1 week, administration of MTX may need to be delayed to avoid the possibility of MTX-induced photodermatitis reactivation. Finally, the review of the literature confirms that the photodermatitis reactivation

reaction is the only well-documented type of photosensitivity due to MTX.

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## METHOTREXATE AND THE PHOTODERMATITIS REACTIVATION REACTION

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