

CASE REPORT

Solar Burn Reactivation Induced by Methotrexate

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Solar burn reactivation, a rare and idiosyncratic drug reaction, has been reported with the use of a variety of drugs. This reaction is believed to be the result of exposure to ultraviolet light during the subsiding phase of an acute inflammatory reaction. It affects areas of the body that have been previously sunburned. We describe a 16-year-old girl who was receiving treatment for acute lymphoblastic leukemia and experienced a second-degree solar burn reactivation reaction to methotrexate. The patient had a mild sunburn on her face and shoulders the day she went to the oncology clinic for her interim maintenance chemotherapy with vincristine 1.5 mg/m²/dose and methotrexate 100 mg/m²/dose. Three days later, she returned to the clinic with a 2-day history of fever ($\leq 100.2^{\circ}\text{F}$), nausea, vomiting, and malaise; the sunburn on her face and shoulders also had become severe, without further sun exposure. Laboratory results revealed elevated blood urea nitrogen and serum creatinine concentrations, and her methotrexate level was elevated at 0.9 mM. The patient was diagnosed with acute renal failure, dehydration, methotrexate toxicity, and second-degree solar burn reactivation reaction. She was admitted to the children's hospital and treated with sodium bicarbonate, acetaminophen with codeine, ondansetron, and silvadene cream. On hospital day 3, the patient's methotrexate level decreased to less than 0.1 mM. The sunburn continued to heal, and after a 14-day hospital stay, complicated by a streptococcal infection, grade 3 mucositis, bacteremia, and mild gastritis and duodenitis, the patient recovered and was discharged. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between the patient's solar burn reactivation and methotrexate. Although methotrexate-induced solar burn reactivation is rare, clinicians should be aware of this potential adverse reaction and consider delaying administration of methotrexate by 5–7 days if a patient reports ultraviolet-related erythema in the past 2–4 days or presents with a notable sunburn.

Key Words: methotrexate, dermatology, solar burn reactivation, photosensitivity, sunburn, toxicity, photoreaction, chemotherapy.

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Solar burn reactivation, a rare and idiosyncratic reaction, is the result of exposure to ultraviolet light and affects areas of the body that have been previously sunburned. This reaction has been reported with the use of a variety of

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chemotherapy agents, including bleomycin, cyclophosphamide, doxorubicin, dacarbazine, dactinomycin, and methotrexate.^{1, 2} Classification of the reaction, however, can be difficult due to the lack of consistent terminology of such reactions.

A few case reports and other published literature describe a severe reactivation of a sunburn after the use of methotrexate; however, this rare adverse reaction is not well known to many clinicians. To my knowledge, no cases of

acute renal failure and elevated methotrexate levels in relation to a solar burn reactivation reaction have been published. We describe a patient who experienced a second-degree solar burn reactivation reaction to methotrexate, which she was receiving as part of a chemotherapy regimen for leukemia.

Case Report

A 16-year-old girl with acute lymphoblastic leukemia presented to the oncology clinic with a 2-day history of fever ($\leq 100.2^{\circ}\text{F}$), nausea, vomiting, malaise, and a severe sunburn on her face and shoulders. Three days earlier, the patient had received interim maintenance chemotherapy with vincristine $1.5\text{ mg/m}^2/\text{dose}$ and methotrexate $100\text{ mg/m}^2/\text{dose}$. At that clinic visit, she had a mild sunburn on her face and shoulders as a result of sun exposure, which was improving. Her serum creatinine concentration was 0.7 mg/dl (normal range $0.7\text{--}1.3\text{ mg/dl}$), and the chemotherapy was administered without incident.

At this clinic visit, physical examination revealed that the patient's lips were dry and cracked, and her sunburn was blanchable, red and purple areas over the face, posterior neck, shoulders, and scapula. Her forehead was peeling, and some areas of small blistering were noted, indicating a second-degree burn. The patient also had dry mucous membranes, and decreased urine output was reported by the patient's family, as well as mild epigastric pain with wrenching episodes. Throat pain and mucositis were not reported. Laboratory results revealed a blood urea nitrogen (BUN) level of 37 mg/dl (normal range $6\text{--}22\text{ mg/dl}$) and serum creatinine concentration of 3.0 mg/dl .

The patient was admitted to the children's hospital. Her baseline urine output was 1.3 ml/kg/hour and absolute neutrophil count (ANC) was 7480 cells/mm^3 (normal $\geq 1500\text{ cells/mm}^3$). Her methotrexate level was elevated at 0.9 mM . The patient was diagnosed with dehydration, acute renal failure, methotrexate toxicity, and a likely solar burn reactivation reaction. She was treated with intravenous fluids and sodium bicarbonate to alkalinize the urine, acetaminophen with codeine for pain, ondansetron for nausea, and silvadene cream for the sunburn.

Improvement was noted in the patient's condition the next day (hospital day 2). After rehydration with intravenous fluids, her creatinine concentration decreased to 2.2 mg/dl , and her urine output increased to 1.9

ml/kg/hour . However, she then developed considerable throat pain. A culture revealed group A *Streptococcus* pharyngitis, and she was treated with intra-muscular penicillin G benzathine 1.2 million units and was given morphine for pain.

On hospital day 3, the patient appeared more ill, still had significant throat pain, and had not had substantial oral intake for 4–5 days. She had developed painful red lesions on both feet secondary to the methotrexate toxicity and had significant pruritis from the sunburn. Intravenous leucovorin 20 mg every 6 hours was initiated to aid in the elimination of methotrexate, which may have caused the acute renal failure. The patient's methotrexate level subsequently decreased to 0.2 mM . In addition, her serum creatinine and BUN concentrations decreased to 2.0 and 17 mg/dl , respectively. Her sunburn began to show signs of healing; however, she continued to have cracked lips and areas of tenderness and erythema on the soles of her feet.

The patient's methotrexate and creatinine concentrations dropped to less than 0.1 mM and 1.5 mg/dl , respectively, on hospital day 4. However, as she continued to experience significant pain related to the photodermatitis, throat infection, and severe mucositis, patient-controlled analgesia with morphine was started. Total parenteral nutrition was also started due to the patient's lack of oral intake secondary to nausea and throat and mouth pain during the hospitalization. On day 5, the patient was diagnosed with grade 3 oral mucositis, and her lips remained cracked and bleeding. However, her ANC continued to decline and was approaching 1000 cells/mm^3 .

Four days later (day 9), the patient received intravenous vincristine and intramuscular peg-asparaginase as part of her chemotherapy protocol. She began feeling better as her sunburn continued to heal, until day 11 when she experienced three episodes of coffee-ground emesis and her fever spiked to 103.8°F . Intravenous pantoprazole 40 mg every 12 hours was started for a suspected gastrointestinal bleed likely secondary to methotrexate toxicity. Cefepime and vancomycin were started for the development of febrile neutropenia. A blood culture revealed coagulase-negative *Staphylococcus*. Due to continued severe epigastric and abdominal pain, an upper gastrointestinal endoscopy was performed on hospital day 13, which showed mild gastritis and duodenitis.

The patient's sunburn resolved, and her lips were crusted and scabbed over. As her ANC had recovered, cefepime was discontinued. She was

discharged on day 14 and prescribed a 10-day course of vancomycin, with hydrocodone-acetaminophen as needed for pain.

Discussion

This patient's case differs from other solar burn reactivation cases described in the literature, as this patient also developed acute renal failure and methotrexate toxicity. On presentation to the clinic, the patient exhibited signs of methotrexate toxicity including nausea, vomiting, malaise, and a solar burn reactivation. However, it is difficult to determine if the cause of the acute renal failure was secondary to methotrexate toxicity or directly related to dehydration, or a combination of these causes. It is also plausible that the dehydration was a direct result of undiagnosed group A *Streptococcus* pharyngitis or was secondary to the development of the severe solar burn reactivation, which lead to acute renal failure and subsequent methotrexate toxicity.

Despite the reported frequency of methotrexate photosensitivity reactions in 5% of patients,³ the literature suggests that the adverse reaction can be more accurately described as a solar burn reactivation or false photosensitivity reaction. A true photosensitivity reaction can be photoallergic or phototoxic. Photoallergic reactions are the result of an immunologic reaction between a drug and ultraviolet light exposure, which interacts with the body's immune system to produce an allergic-like reaction resembling acute or chronic dermatitis that affects exposed skin, but may also spread to unexposed skin. This reaction typically occurs more than 24 hours after exposure. A phototoxic reaction is the result of a photoactive substance in the skin being activated by ultraviolet light. These substances are then transferred to the surrounding areas of skin tissue, resulting in damage to the skin resembling a severe sunburn in areas that were exposed to sunlight. Phototoxic reactions tend to occur within minutes to hours of exposure to the substance and ultraviolet light.¹

Solar burn reactivation does not fit the description of photoallergic or phototoxic reactions. Solar burn reactivation tends to occur during the subsiding phase of a sunburn, after exposure to a drug, and can occur up to 7 days after the original sun exposure occurred.⁴⁻⁷ It has been proposed that exposure to the drug causes an enhancement of the inflammatory reaction, resulting in a reactivation and exaggeration of a sunburn in the areas that were

exposed. Other literature suggests that the mechanism is associated with an increased rate of basal cell proliferation after solar erythema and the subsequent destruction of hyperproliferating basal cells after chemotherapy.⁴

The pathogenesis of methotrexate-induced solar burn reactivation is not well understood, but it is thought to be related to ultraviolet A- and ultraviolet B-ray exposure and intracellular damage to DNA. The reactivation of a sunburn due to methotrexate was first observed in 1965.⁷ Four years later, a researcher induced erythema of the skin in patients with psoriasis using a high-pressure mercury-arc lamp before administering methotrexate.⁶ He found that patients who were irradiated 2-4 days before receiving methotrexate experienced a flare up of erythema. Patients who were irradiated simultaneously with methotrexate or 4 days before ultraviolet light exposure showed no reactivation of erythema. Based on his discovery, it became apparent that methotrexate had the ability to reactivate a receding inflammatory process, resulting in a solar burn reactivation.

One case report described a "severe reactivation of sunburn" caused by methotrexate in a 13-year-old boy being treated for non-Hodgkin's lymphoma.² The child experienced tingling and burning at the sites of his resolving sunburn shortly after receiving methotrexate. For 2 days, the burn progressed to marked erythema, edema, vesiculation, and great discomfort. In contrast, the 16-year-old patient described in this case report did not experience any tingling or burning around the time of methotrexate administration, but she did develop a severe burn 2 days later, which is consistent with the timeline of erythema reactivation in the 13-year-old patient.²

Erythema reactivation may be a dose-related phenomenon.⁸ However, published case reports have described solar burn reactivation with a wide variety of methotrexate doses, ranging from as low as 2.5 mg/kg to 250 mg/kg, whereas some authors reported only high-dose methotrexate, without giving the specific dose.^{2, 4, 9-12} The patient in this case report, however, was receiving a low dose of methotrexate; thus, this adverse reaction does not appear to be dose related.

Leucovorin therapy was initiated in this patient to aid in methotrexate elimination. This was done to prevent further methotrexate-induced toxicities, including nephrotoxicity. Leucovorin rescue was found to be highly effective in patients after the onset of methotrexate-induced nephrotoxicity and delayed methotrexate

excretion.¹³ However, as reported in 1976, the use of leucovorin rescue after a solar burn does not prevent a solar burn reactivation reaction.⁵

Studies have also shown that the combination of L-asparaginase and methotrexate has synergistic antileukemic activity when given on a particular schedule to maximize cytotoxicity, while providing a means of methotrexate rescue.¹⁴⁻¹⁶ When L-asparaginase is administered after methotrexate, it has been shown to stop both methotrexate's therapeutic and toxic effects by interfering with protein synthesis and decreasing methotrexate polyglutamation, thus decreasing toxicity.¹⁴⁻¹⁶ Many oncologic drug regimens use this advantageous drug interaction during interim maintenance to provide some form of rescue for patients with methotrexate toxicity, as hydration and leucovorin are often not provided during this phase of treatment. In the patient in this case report, the administration of peg-asparaginase on day 9 may have contributed to the healing and recovery of the methotrexate toxicity due to the drug interaction and the ability for L-asparaginase to decrease methotrexate polyglutamation.

Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between the patient's solar burn reactivation and methotrexate.¹⁷ To fit the definition of a probable reaction, the adverse drug reaction had to fit the following criteria: followed a reasonable temporal sequence after drug administration, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state.¹⁷

The timing of our patient's solar burn does not fit the definition of a photoallergic or a phototoxic reaction. In addition, she presented 2 days after receiving the methotrexate infusion with a second-degree burn in areas of a mild sunburn that had occurred 3 days before presentation. The sunburn appeared to be subsiding when the methotrexate was administered, which fits the definition and timing of a solar burn reactivation, as well as the mechanism of its occurrence.

Conclusion

This patient presented with a solar burn reactivation, fever, and acute renal failure approximately 2 days after exposure to methotrexate. The actual cause of her acute

renal failure and methotrexate toxicity appear to be multifactorial; however, the development of the second-degree solar burn reactivation may have played a role. Although methotrexate-induced solar burn reactivation is rare, it is important that clinicians are aware of this potential adverse reaction and consider delaying the administration of methotrexate by 5–7 days if a patient reports ultraviolet-related erythema in the past 2–4 days or presents with a notable sunburn.

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