

Teaching Case

Radiation Recall Dermatitis After the Use of Pralatrexate for Peripheral T-cell Lymphoma

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Received 25 July 2018; revised 31 August 2018; accepted 1 October 2018



Introduction

Radiation recall dermatitis (RRD) is a well-known but poorly understood phenomenon. This clinical entity is uncommon with an estimated incidence of 1% to 10% in patients who receive systemic agents after radiation therapy (RT).

RRD is an inflammatory reaction of the skin that occurs in a previously irradiated area shortly after the administration of a systemic agent. Skin changes can range from erythema to erosions and frank ulcerations.¹ RRD may be related to radiosensitization, but is distinguished by the timing of the precipitating agent after completion of RT. Generally, the systemic agent should be administered at least 7 days after RT completion for any toxicity to be considered a radiation recall effect. RRD is an inflammatory process that begins after drug administration rather than an enhancement of the primary reaction to RT. In fact, cases of RRD have been reported years after patients have completed RT. RRD can result in significant skin toxicity that warrants clinical intervention.²

Pralatrexate is a novel, targeted, antifolate agent that was approved by the U.S. Food and Drug Administration in 2009 for the treatment of relapsed or refractory

peripheral T-cell lymphoma (PTCL).³ Similar to methotrexate, pralatrexate is a dihydrofolate reductase inhibitor but with a higher affinity for the reduced folate carrier expressed at high levels in cancer cells.⁴ The most common toxicities reported in the Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma trial included fatigue, nausea, thrombocytopenia, and mucositis. Approximately 15% of patients in that trial experienced a skin rash or pruritus, and only 2 patients experienced grade 3 pruritus.⁵

Multiple agents have been associated with RRD, but there is no published report of pralatrexate causing RRD. We report on a case of palliative RT delivered in between cycles of pralatrexate therapy for PTCL that resulted in ulceration (grade 3 skin toxicity) of previously irradiated lateral left hip and anterior left thigh regions.

Case Presentation

A 74-year-old woman was diagnosed with PTCL after developing deep-seated tumors in her lower back and left upper thigh. The patient received methotrexate for 3 months followed by brentuximab vedotin for 3 months. Unfortunately, 2 years after presentation, she experienced progression after 2 lines of systemic therapy.

Subsequently, the patient was noted to have an approximately 1 cm indurated nodule with central ulceration on the left anterior thigh, as well as a 3 cm hyperpigmented indurated plaque with superficial erosion on the left lateral hip (Figs 1A-B).

Sources of support: This work had no specific funding.

Conflicts of interest: The authors have no conflicts of interest to disclose.

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<https://doi.org/10.1016/j.adro.2018.10.001>

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Figure 1 Photographic progression of patient's skin lesions at the (A) anterior left thigh and (B) lateral left hip. Photographs were taken at initial presentation to radiation oncology, after 5 weeks of pralatrexate therapy post-radiation therapy, and 7 weeks after discontinuation of pralatrexate.

The patient's treatment was changed to pralatrexate. Each cycle of treatment consisted of the weekly intravenous administration (30 mg/m^2) of the medication for 6 weeks. At the end of the first cycle, the dermal lesions on the anterior left thigh and lateral left hip areas progressed, but other areas of the disease had responded to treatment. One week after the first cycle, the patient received external beam RT to the left thigh and hip using a 3-dimensional conformal technique. Two slightly oblique antero-posterior fields were used to include both the left thigh and hip lesions with a 2 cm margin (Fig 2). The total dose delivered was 2200 cGY in 5 fractions.

Seventeen days after her last radiation treatment, the patient started her second cycle of pralatrexate therapy ($30 \text{ mg/m}^2/\text{wk}$). Within 2 days of resuming pralatrexate, the patient noticed worsening erythema, desquamation, and ulceration in both the anterior left thigh and lateral left hip regions within the radiation field. At the next follow-up visit, the patient had completed 5 weeks of pralatrexate

therapy but developed progressive ulcers of the previously irradiated skin lesions and grade 3 oral mucositis (Figs 1A-B).

Because of these toxicities, the patient's pralatrexate treatment was discontinued. Culture swabs of the skin lesions were taken and did not reveal evidence of infection. The patient's skin lesions were treated with topical timolol and mupirocin. One month later, the patient reported that the skin lesions were healing well (Figs 1A-B).

Discussion

This is the first reported case of pralatrexate-associated RRD. Clinicians across disciplines, including radiation oncologists, hematologists, medical oncologists, and dermatologists, should be aware of the possibility of RRD when pralatrexate is administered after RT.

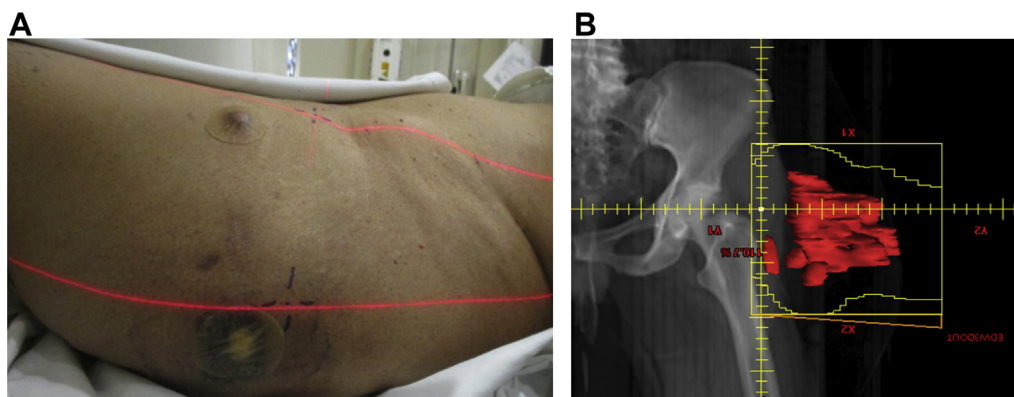


Figure 2 (A) Simulation set-up photo showing anterior left thigh and lateral left hip lesions. (B) Digitally reconstructed radiograph demonstrating anterior field with tumor outlined in red.

Other antifolate drugs have been previously associated with RRD (Table 1). Thus, antifolate medications may be associated with RRD as a class, and RRD after the administration of any medication with a similar mechanism of action would be reasonable to consider. The severity of skin reactions may vary from erythema to skin to tissue necrosis that requires surgical intervention. Other common side effects of pralatrexate include mucositis, thrombocytopenia, nausea, fatigue, and liver function test abnormalities.⁵ Of note, our patient experienced mucositis, a non-RT-related toxicity, during the time of the recall reaction. Underreporting of non-RT-related side effects is a possibility, but a review of the literature did not find an association of the incidence and severity of these toxicities with the development of RRD. Future case reports should include other toxicities that occur around the time of the recall reaction to provide more information on the possible association between RRD and other non-RT-related toxicities.

Radiation dose, drug dose, and time interval to drug exposure have all been postulated as risk factors for developing RRD.² However, the literature on RRD is

primarily composed of case reports that have demonstrated a wide variety of dosing regimens and time intervals, making the establishment of specific thresholds difficult. In antifolate-associated cases of RRD, the time interval to drug exposure has been as long as 25 years, and total radiation doses have ranged from 20 Gy to 60 Gy (Table 1). Moreover, radiation recall can affect any previously irradiated area, including soft tissues and internal organs (resulting in toxicities such as gastritis, stomatitis, and myositis).¹ Beyond antifolate medications, RRD has been most commonly associated with anthracyclines (doxorubicin), taxanes (docetaxel, paclitaxel), and antimetabolite agents (gemcitabine, capecitabine).¹

Treatment for RRD includes the discontinuation of the offending medication and supportive care.¹ Our patient experienced wound healing soon after discontinuation of pralatrexate. Topical corticosteroid and nonsteroidal antiinflammatory medications may also be helpful to minimize inflammation. The literature does not provide enough guidance with regard to altering prospective radiation doses, drug dose, or time to drug exposure to decrease the risk of RRD as mentioned earlier.

Table 1 Summary of antifolate drug associated RRD cases

Drug	No. of Cases	Drug dose (range)	RT dose (range)	Time to drug exposure from RT (range, at least 7 days)	Time from drug exposure to reaction (days)	Type of skin reaction (range)	Number of cases with drug rechallenge	Skin reaction intensity on rechallenge compared with initial reaction	Comments
Edatrexate ⁶	1	100 mg/m ²	30 Gy	4 weeks	7 weeks	Erythema with vesicular eruption	1	Less intense	
Methotrexate ⁷⁻¹¹	5	10-350 mg/m ²	20-40 Gy	8 days to 6 weeks	2-7 days	Erythema, erosion, ulceration	3	2 less intense, 1 not stated	2 cases without time to drug exposure specifically stated, ¹¹ 1 case reported with concurrent cyclosporine, ⁸ 1 case with cyclophosphamide and 5-fluorouracil ¹⁰
Pemetrexed ¹²⁻¹⁷	5	500 mg/m ²	21-60 Gy	19 days to 25 years	3-28 days	Erythema with edema, erosion, ulceration, and skin/soft tissue necrosis	4	1 no reaction, 1 less intense, 1 similar reaction, 2 more intense	2 cases with concurrent cisplatin, ^{13,15} 1 case not included as time to drug exposure from RT was <7 days ¹⁶
Pralatrexate	1	30 mg/m ²	22 Gy	17 days	2 days	Erosion and ulceration	0	NA	Current report

Abbreviations: NA = not available; RT = radiation therapy.

Rechallenge of the precipitating drug has been tried, with a majority of patients experiencing a skin reaction on rechallenge, but these may be less severe compared with prior treatment.² Potential approaches to decrease the risk of RRD on rechallenge include decreasing medication dose and premedication with steroidal medications.

Conclusions

RRD is a clinically significant event that should be recognized when any skin reaction develops in a previously irradiated area after the administration of a systemic agent. When increasing the utilization of pralatrexate, clinicians should be mindful of RRD when prescribing the medication after patients have undergone RT.

Acknowledgments

The authors thank the patient and the patient's family for granting permission to publish this case report.

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