



Systemic methotrexate for prurigo nodularis and keratoacanthomas in actinically damaged skin

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INTRODUCTION

We previously reported a cohort of elderly patients with concurrent development of debilitating prurigo nodularis, extreme and disabling pruritus with or without eczematous dermatitis, and keratoacanthomas in the presence of actinic damage.¹ This report is a long-term follow through on patients who were successfully transitioned from cyclosporine, acitretin, and topical 5-fluorouracil to subcutaneously administered methotrexate. We believe that an underlying dysregulation of both inflammatory and cell growth pathways predisposes these individuals to the development of both types of lesions.¹ Three of the patients have since been successfully treated with systemic methotrexate and are described below. We stated in our original report that no patients had keratoacanthomas while on cyclosporine and acitretin; however, in reviewing the material for this follow-up report, keratoacanthomas were noted in the patients' files. These lesions were existing lesions that did not clear after the initiation of therapy and were deemed suspicious enough for further evaluation. Herein we describe patients who underwent transition from cyclosporine to methotrexate and experienced relief of their symptoms.

Traditional treatment options for keratoacanthomas include standard excision, Mohs micrographic surgery, systemic retinoids, radiotherapy, curettage and electrodesiccation, and intralesional 5-fluorouracil.² In patients with a predisposition to the development of pruritic nodules and multiple keratoacanthomas, many of the aforementioned treatments are ineffective or only elicit some clinical response, often with relapse.¹

Intralesional methotrexate is noted in the literature as an effective and well-tolerated treatment for solitary keratoacanthomas.²⁻⁴ However, this approach may not be practical in the case of multiple keratoacanthomas, especially if it is believed that a predisposition exists for the development of additional lesions, as is the case in our patients.¹ Systemic methotrexate, used for rheumatoid arthritis⁵ and psoriasis,⁶ has also been reported as an effective treatment for prurigo nodularis.⁷ Some literature supports the use of parenteral methotrexate as a method to ensure uniform and predictable bioavailability, particularly in doses at and greater than 15 mg.⁸⁻¹² We have also observed that accessibility of injectable methotrexate is far more affordable than the oral tablet form, and patients are less likely to confuse their dosing regimens with the subcutaneous format.

To our knowledge, there are no reports on the use of systemic methotrexate to treat keratoacanthomas. Three distinct cases are described in this report.

METHODS

We reviewed all cases of keratoacanthomas associated with prurigo nodularis that were treated with methotrexate at the New York University Langone Medical Center between January 2000 and April 2015. Inclusion criteria included keratoacanthomas, prurigo nodularis, and treatment with methotrexate along with folic acid supplementation. A keratoacanthoma was defined as any histologically confirmed keratoacanthomas or squamous cell carcinoma that was clinically crateriform, nodular, or dome shaped. The presence of prurigo nodularis

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was defined as histologically confirmed prurigo nodules or a pruritic lesion in the setting of a histologically confirmed hypersensitivity reaction.

Analysis of the subjects' charts included age, sex, ethnicity, reason for visit, relevant history, course of disease, treatments and doses, length of treatment, adverse events, reason for discontinuation, characteristics of biopsies, and unidentified localized photographs. Itching severity was not gauged by the Visual Analog Scale or other visual scoring system. Patients related incapacitating itch that resulted in interference with activities of daily living, and, in every patient, deep excoriations were present in affected surface areas. Improvement was determined based on alleviation of these factors as mentioned in patient charts. The study was approved by New York University School of Medicine's Institutional Review Board.

RESULTS

Case 1

A 78-year-old woman presented with biopsy-proven eczematous dermatitis and prurigo nodularis and a clinical picture consistent with eruptive keratoacanthomas. She was treated with prednisone, topical corticosteroids, tacrolimus, and emollients over the year and a half prior to her presentation, but none were more than temporarily helpful. She was started on cyclosporine and acitretin, which resulted in marked decrease in erythema, scale and induration. After 6 weeks on cyclosporine and acitretin, there was a marked reduction in all skin lesions with 2 prominently persistent keratotic papules that were consistent with keratoacanthomas and squamous cell carcinoma on biopsy results. Over the next 4 years, even when cyclosporine was held intermittently and eventually discontinued, some smaller but persistent lesions were found to be keratoacanthomas. Acitretin was later discontinued because of leg cramps.

Nearly 4 years after her initial presentation, the patient still had many excoriated nodules and plaques on the trunk and extremities. Weekly intramuscular injections of 12.5 mg were started, and there was a noticeable decrease in scale, crust, and induration after 3 weeks. The patient also used a topical compound containing triamcinolone acetonide and pramoxine/hydrocortisone throughout the course of methotrexate and 5% 5-fluorouracil nightly to individual lesions in a 2 months on, 1 month off regimen. Nine months into methotrexate treatment, the patient remains markedly improved with a decrease in number of lesions and induration of each lesion and no new keratoacanthomas.

Case 2

A 78-year-old woman presented with eczematous dermatitis and prurigo nodularis in sun-exposed areas for 8 months, having been unsuccessfully treated with topical steroids, prednisone, and emollients. The patient was started on cyclosporine and showed some improvement. Six weeks later, her eczematous dermatitis was well controlled, but eruptive keratoacanthomas started to develop, and cyclosporine was discontinued. She continued acitretin for more than 3 years and was concurrently treated with 8 months of mycophenolate mofetil and levocetirizine, 8 months of oral tacrolimus, and liquid nitrogen to individual lesions. These treatments were somewhat efficacious in reducing the extent of excoriation; however, an infiltrating squamous cell carcinoma developed while on tacrolimus and continued to worsen over the next year.

Four years after her original presentation without marked improvement, she began 10 mg of weekly oral methotrexate without the aforementioned therapies. After 1 month there was substantial improvement in erythema and excoriations, and the dose was increased to 15 mg weekly in the form of subcutaneous injections. There was further improvement after an additional 10 weeks, but the patient reported nausea and an incidence of diverticulitis, so the dose was decreased to 12.5 mg/wk. Two weeks later, methotrexate was discontinued entirely because of nausea and loss of appetite. After 2 weeks off the methotrexate, new areas of erythematous plaques and excoriations developed, and the patient requested to restart treatment. Later that month, however, the patient was hospitalized for an infection, and the methotrexate was discontinued. New lesions developed since stopping treatment, but she remains off methotrexate for now because of these adverse events.

Case 3

An 80-year-old woman with a history of squamous cell carcinoma presented with eczematous dermatitis and prurigo nodularis that was treated with fexofenadine, emollients, and clobetasol with limited success. Because of the development of widespread erythema and keratotic plaques, the patient began acitretin and cyclosporine. After 1 month on cyclosporine, an infiltrating squamous cell carcinoma with features of keratoacanthoma was biopsied, and the dose of cyclosporine was reduced. After some initial improvement on the new dose, the patient presented 4 months later with worsening prurigo nodularis, eruptive keratoacanthomas, and actinic keratoses. She continued cyclosporine and acitretin for 10 months until discontinuing the

acitretin because of eye pain and irritation. During that time, one basal cell carcinoma developed on the forehead. While continuing cyclosporine, the patient was concurrently treated with 2 months of narrow-band ultraviolet B therapy, intralesional methotrexate, intralesional triamcinolone, and 8 months of mycophenolate mofetil, all without efficacy.

More than 3 years after her initial presentation, the patient still suffered from eruptive keratoacanthomas and prurigo nodules. Cyclosporine and mycophenolic acid were discontinued, and the patient began weekly subcutaneous injections of 15 mg of methotrexate. The patient had decreased plaque thickness and quantity and improved itch about 7 weeks into treatment, and her dose was reduced to 10 mg/wk after 15 months of treatment. She has intermittent follicular eruptions controlled with bleach baths and desonide cream but has otherwise been under good control.

DISCUSSION

Compared with cyclosporine in this small series, methotrexate seems to yield marked improvement with less potential risk for new lesion development. Cyclosporine reduces the activation of various cytokines and suppresses both the cell-mediated and humoral immune responses and interferes with leukocyte recruitment.^{13,14} Despite these immunosuppressive and anti-inflammatory effects, new lesions developed infrequently, and more often prior lesions failed to involute in our patients. This finding may be explained by cyclosporine's suppression of the immune surveillance system and possible stimulation of transforming growth factor beta.¹⁵ It has been noted in the literature that cyclosporine is associated specifically with an increased risk for cutaneous squamous cell carcinoma.¹⁶

Methotrexate has a lesser carcinogenic effect because of its antiproliferative properties.¹⁷ Low-dose methotrexate is also found to have anti-inflammatory properties, although the mechanism is not well understood. Recent investigations suggest that this finding is owing to blockade of certain pathways leading to an increase in adenosine, which has potent anti-inflammatory effects.¹⁸ Despite the antiproliferative properties, increased risk of cutaneous squamous cell carcinoma is associated with high-dose methotrexate therapy.¹⁹ However, this finding does not seem significant in patients receiving low-dose methotrexate, as used in our series, and no such lesions developed during treatment. The quandary of the intractably itchy patient, unresponsive to standard topical therapies in the setting of carcinomatosis poses a vexing clinical scenario. Subcutaneous methotrexate in the absence

of absolute contraindications may provide relief of the prurigo lesions while assuaging the pruritic symptoms without increasing the development of keratoacanthomas in these high-risk patients.

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