Treatment of Palmoplantar Keratoderma With Continuous Infusion 5-Fluorouracil

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GOAL

To provide effective drug treatment for inherited punctate palmoplantar keratoderma (PPK)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the clinical presentation of PPK.
2. Describe the treatment options for patients with PPK.
3. Discuss the evidence-based support for using continuous infusion 5-fluorouracil to treat patients with PPK.

CME Test on page 326.

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A 49-year-old man electively chose to undergo a trial of intravenous chemotherapy with 5-fluorouracil (5-FU) for his inherited punctate palmoplantar keratoderma (PPK). His father also had this skin disorder, which coincidentally cleared after 2 courses of chemotherapy consisting of 5-FU and cisplatin to treat his lung cancer, prompting the patient to undergo this trial of therapy. After the patient's first course of a 5-day continuous infusion (CI) of 5-FU (1000 mg/m^2 per day), the lesions on his hands and feet regressed by approximately 80%. However, after completion of each course, the lesions seemed to reappear to some degree. The patient desired to pursue further therapy; therefore, CI 5-FU at a dose of 250 mg/m^2 per day (500 mg/d) was instituted, while pyridoxine was avoided in the hope of causing a hand-foot syndrome that may provide

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some long-term benefit. After receiving a 12-week course of therapy of CI 5-FU at 250 mg/m² per day, his lesions were approximately 95% improved, with only a few minute punctate keratoses remaining. At follow-up nearly 4 years later, the lesions remain 90% cleared.

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Although, to our knowledge, there has been no literature that associates systemic 5-fluorouracil (5-FU) with the treatment of palmoplantar keratoderma (PPK), we are convinced that systemic 5-FU was responsible for clearing the lesions in a patient—possibly due to the epidermal changes in the palms and soles secondary to hand-foot syndrome induced by 5-FU.

An objective assessment of our patient suggested that systemic 5-FU most likely was the reason for the apparent clearing of his keratoses; however, a randomized controlled trial is needed to determine if systemic 5-FU is applicable in the treatment of PPK. This case brings new light to a disease for which treatment options are limited and no cure exists.

PPK represent a heterogeneous group of disorders most often characterized by a hyperkeratosis of the palms and soles.[1,2] PPK may be hereditary, acquired, or an associated feature that is part of a syndrome. Clinically, inherited PPK can be divided into 3 forms: diffuse, striated, and punctate.[3]

The pathogenesis of PPK remains unknown, and the treatment is purely symptomatic; there is no definitive treatment or cure.[4] Treatment modalities have consisted of topical and systemic therapy as well as surgical excision. The literature has indicated no major benefits with the use of topical therapy, including topical retinoids, corticosteroids, calcipotriol, or topical keratolytics such as 5% to 10% salicylic acid ointment, 30% propylene glycol, 20% to 30% lactic acid, and 10% to 12% urea ointment.[1,5-7] Keratolytic agents may be useful in reducing the thickness of the keratoderma, but the lesions recur when treatment is stopped.[6] Overall, the outcomes of treatment of PPK have been rather disappointing. Superior results from systemic treatment with oral retinoids, specifically isotretinoin, have been reported in some cases of PPK. However, there are significant risks and toxicities associated with long-term oral retinoid therapy; and like keratolytic agents, discontinuance of therapy causes the lesions to recur to their initial severity.[1,7]

We report a case of inherited punctate PPK treated successfully with systemic 5-FU. Prior to this, the patient had tried treatment with many topical keratolytic agents, including salicylic acid, urea, and topical 5-FU, from which he attained only minimal benefit. The option of therapy with oral isotretinoin was discussed with the patient; however, he did not choose this option because it is not a cure and lifelong treatment would be required for long-term benefits.

Case Report

A 49-year-old man electively chose to undergo a trial of intravenous chemotherapy with 5-FU for his punctate PPK. He had had this dermatologic disorder since he was a teenager. The patient reported that the calluses on his feet were painful and that those on his hands were embarrassing. Differential diagnosis ruled out toxin-induced PPK (ie, arsenic) because of the lack of chemical exposure; he was diagnosed with hereditary punctate PPK, of which his family history is significant (his father also had the disorder). In 1987, his father was diagnosed with lung cancer and received chemotherapy consisting of continuous infusion (CI) 5-FU and cisplatin. Coincidentally, his lesions cleared after 2 treatments and never recurred, though he died of lung cancer 2 years later.

The patient's dermatologist noted that treatments had been unsuccessful thus far and that therapeutic options had been exhausted. The dermatologist was unaware of alternative treatments and thoroughly reinforced to the patient that other than his father's case, there was no evidence to suggest that treatment with 5-FU was effective. The patient was aware that systemic 5-FU was not the standard of care for PPK; however, he was willing to accept all risks associated with treatment.

Prior to initiating therapy, the patient weighed 81 kg and was not taking any medications including topical creams and over-the-counter products. His medical history was significant for back problems and a herniorrhaphy. He smoked three quarters of a pack of cigarettes a day. His mother died of heart disease. His siblings were alive and well.

The patient's laboratory results were acceptable to start treatment. A peripherally inserted central catheter line was placed. Pictures were taken of the lesions before treatment to document possible response. A single course of CI 5-FU was instituted: 1000 mg/m² per day for 5 days via an infusion pump connected to his catheter line. The patient was instructed to gargle daily with 0.5% hydrogen peroxide solution.

The patient tolerated the first course of 5-FU without incidence. Other than minor fatigue and slight mucositis, he experienced no particular side effects, though he noticed his feet were more painful than usual. Physical examination revealed

mild erythema over his hands, and some of the lesions that used to be skin colored were now purplish and erythematous.

At his 1-month follow-up, the patient was pleased that the lesions over his hands and feet had regressed remarkably after only one treatment. The oncologist and patient agreed that the lesions had been reduced by approximately 80%. Laboratory tests disclosed the following values: a white blood cell count of 5400/mm^3, a hemoglobin level of 15.5 g/dL, and a platelet count of 194,000/mm^3. It was clearly reiterated to the patient again that there was no evidence to suggest that treatment with intravenous 5-FU was effective, despite encouraging results.

After 2 courses of CI 5-FU at 1000 mg/m^2 per day for 5 days, the patient desired to pursue further treatment because after each course the lesions seemed to grow back to some degree, though they remained about 75% improved. Because the patient was adamant about pursuing further therapy, CI 5-FU was dosed at 250 mg/m^2 per day in the hope that he might develop some hand-foot syndrome, which may lead to long-term benefits. The full course of treatment would require several weeks; thus, a port-a-cath was surgically placed and connected to an infusion pump that administered 5-FU continuously.

After a 12-week therapeutic regimen of 250 mg/m^2 per day of CI 5-FU, the patient's lesions were approximately 95% cleared and, for the most part, were unapparent. He had no significant side effects from the 5-FU other than mild cheilosis. Two months later, the lesions had not returned. At follow-up nearly 4 years later, the dermatologist rated the lesions as being 90% cleared; however, the patient believes that the lesions are 100% cleared with only scar tissue remaining. The Figure demonstrates the effectiveness of treatment.

The patient has experienced one adverse effect since the time 5-FU was initiated, ie, an increased dermatologic sensitivity to non–glycerin-based soaps and shampoos. However, by switching to glycerin-based products, the problem disappeared. Although it is not known whether treatment with 5-FU was the sole culprit of this problem, the timing of treatment and onset of the sensitivity suggest an association.

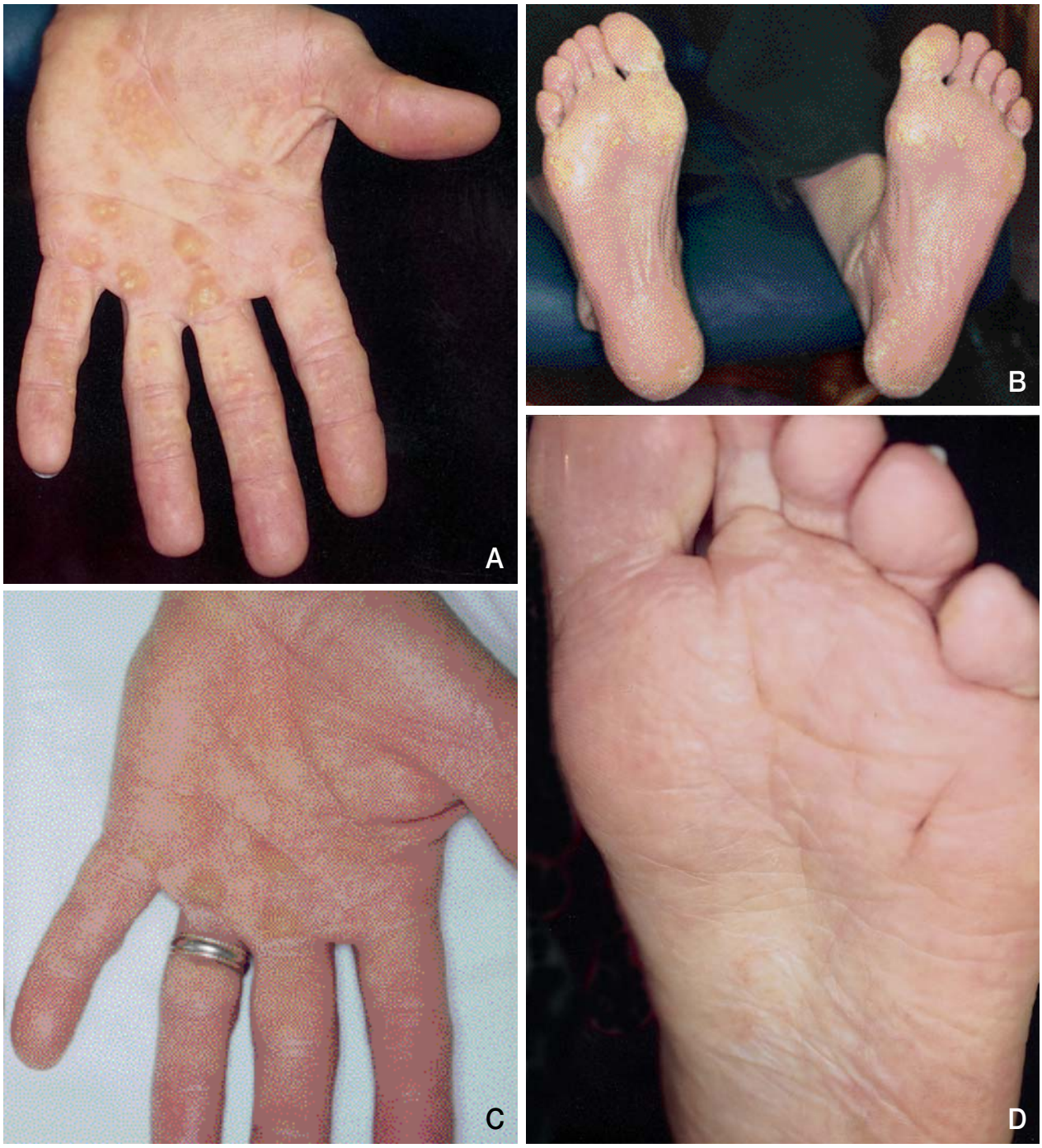
Comment

In 1879, Davies-Colley described punctate PPK as "disseminated clavis of the hands and feet."[3,8] Punctate PPK also is referred to as keratosis punctata palmaris et plantaris or Buschke-Fischer-Brauer disease.[6,9] Although the incidence in the United States is unknown, the reported incidence for this rare genodermatosis is 1.17 per 100,000 people in Croatia.[10] Hereditary PPK is autosomal dominant and usually develops when a patient is between 12 and 30 years of age.[3,11] Punctate PPK presents with abundant hyperkeratotic papules on the palms and soles that are irregularly distributed. The papules tend to be asymmetric, vary greatly in size, and occur more frequently over pressure points, causing pain in many cases.[3,6,9] To our knowledge, there have been no cases of spontaneous remission in patients with inherited PPK.

For years, retinoid therapy has represented the treatment of choice for severe inherited keratodermas.[12] Treatment of punctate PPK, specifically, usually consists of topical retinoids or calcipotriol to soften the keratoses, and systemic retinoid therapy, if warranted. Although topical tretinoin (vitamin A acid) has been proven to be effective in many keratinizing dermatoses, Muller et al[13] revealed that topical tretinoin 0.1% cream was not effective in palmar-plantar hyperkeratosis. In the early 1980s, Bergfeld et al[1] demonstrated that oral isotretinoin, a vitamin A analogue, was effective in treating a variety of keratinizing disorders, including one case of punctate keratoderma. Despite the "antikeratolytic" effects of isotretinoin, disease relapse occurred with a reduced retinoid dose and symptoms fully recurred after therapy was discontinued. Oral retinoid therapy is not a cure; therefore, treatment must be continued indefinitely to maintain results.

Topical 5-FU has been used to treat actinic keratoses and basal cell carcinomas.[14,15] Osman et al[5] reported a case of "spiny keratoderma of the palms and soles" that responded well to 5-FU 5% cream. Recently, a study performed by Levy et al[16] suggested that 5-FU 0.5% cream compared with 5-FU 5% cream is equally effective, is associated with less toxicity and may actually be more specific to the affected area of skin in which the cream is applied. These conclusions, though counterintuitive, stem from higher concentrations of 5-FU found in the skin following application of the 0.5% cream compared with the 5% cream. This data is applicable for actinic keratoses; however, it is not clear whether PPK would require higher concentrations of topical 5-FU. The patient in our case, as previously mentioned, experienced only minimal response with topical 5-FU 5% cream. To our knowledge, there has been no evidence that associates systemic 5-FU therapy for treatment of PPK.

In vivo, the mechanism of 5-FU is quite complex. Depending on whether the tissue type is normal or a tumor, the compound will exert a different action.[17] Cells proliferating at a rapid rate, especially solid



Palmar keratoderma prior to (A and B) and after (C and D) treatment with continuous infusion of 5-fluorouracil.

tumors, are more of a target for the toxic effects from 5-FU than are nonproliferating cells.[15] Systemic therapy with 5-FU can cause a variety of dermatologic manifestations, such as maculopapular eruption, hyperpigmentation, nail changes, lupuslike butterfly rash, inflammation of actinic keratoses, and palmar-plantar erythrodysesthesia syndrome (PPES), also known as hand-foot syndrome.[18] Clinically, these changes can be categorized into 3 subsets: rashes and eruptions, cytotoxic changes, and alterations in pigmentation.[18,19]

Hand-foot syndrome is characterized by a "tingling sensation" of the palms and soles. It starts out as dysesthesia, and after a few days, there is a burning

pain associated with swollen palms and soles that are erythematous, cracked, and eruptive. In severe cases, ulceration and blistering can occur followed by desquamation.[18-20] Treatment with pyridoxine (100–150 mg/d) has been proven to be effective in preventing PPES or in making the symptoms less severe without having to discontinue 5-FU therapy.[18,21] Therefore, pyridoxine should be avoided if hand-foot syndrome is a desired outcome, such as in our case.

The specific mechanism by which 5-FU causes PPES remains unknown, and the specific distribution on the palms and soles also is poorly understood. However, it has been hypothesized that PPES is a "direct toxic effect of the chemotherapeutic drug against epidermal cells" and, thus, PPES is the result of a cytotoxic reaction that mainly affects keratinocytes.[22] The epidermis of the palms and soles are highly proliferative, making it a target for 5-FU to induce changes within the epidermis—making it more susceptible to PPES.[15] Histologic findings in the basal cell layer of the skin include a variable degree of epidermal necrosis and poor cell infiltrate. Changes in the epidermis consist of vasodilation of the blood vessels and papillary edema from the mechanical and thermal trauma.[22,23]

Two meta-analyses of frontline trials for advanced colorectal cancer compared and evaluated the efficacy and toxicities of intravenous CI 5-FU versus bolus administration. With the exception of hand-foot syndrome, the meta-analysis revealed that CI 5-FU was associated with a significant reduction in grade 3 or 4 hematologic and nonhematologic toxicities (4% vs 31%), but there was an increased incidence of hand-foot syndrome with CI 5-FU compared with bolus administration (34% vs 13%).[24,25]

There is little, if any, data to support or guide therapy duration; therefore, the basis for treatment length was determined by oncologist and dermatologist observations of drug effect, lack of adverse effect, and willingness of the patient to continue therapy. Treatment was discontinued when it appeared that it had been fully successful, which was approximately 12 weeks for our patient.

Although our patient experienced only mild side effects, 5-FU has the potential to cause serious adverse effects. The earliest of milder untoward effects include anorexia and nausea followed by stomatitis and diarrhea. Mucosal ulcerations may occur throughout the gastrointestinal tract, particularly in patients receiving continuous infusions of 5-FU; these ulcerations can lead to fulminant diarrhea and hypovolemic shock.[26] Myelosuppressive effects are more common with bolus administration of 5-FU than with CI and include leukopenia, thrombocytopenia, and anemia.[26] Neurologic manifestations, including acute cerebellar syndrome, have been reported, as have reports of cardiac toxicity, particularly acute chest pain with ischemia.[26]

Cisplatin was ruled out as being a contributory factor in the clearing of the patient's father's keratoses. Other than alopecia, cisplatin is known to have minimal dermatologic effects. However, Lee et al[27] reported a case of cisplatin-induced severe allergic exfoliative dermatitis associated with ischemia and necrosis of the hands. The adverse effects and toxicities associated with cisplatin are well recognized and include immunosuppression, neurotoxicity, nausea and vomiting, ototoxicity, and hypomagnesemia.[27]

Conclusion

An objective assessment of our patient suggested that systemic 5-FU was the most likely reason for the apparent clearing of this patient's keratoses. However, a randomized controlled trial is needed to determine if systemic 5-FU is applicable in the treatment of PPK. This case brings new light to a disease for which treatment options are limited and no cure exists.

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