Keratosis Punctata Palmoplantaris Controlled With Topical Retinoids: A Case Report and Review of the Literature

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GOAL

To understand the various forms of palmoplantar keratodermas (PPKs)

OBJECTIVES

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

1. Explain the clinical presentations of the various forms of PPK.
2. Discuss the histology of the various forms of PPK.
3. Examine the treatment options for keratosis punctata palmoplantaris.

CME Test on page 180.

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Keratosis punctata palmoplantaris (KPPP) is a rare genodermatosis with an autosomal-dominant pattern of inheritance. We report the case of a 61-year-old woman who presented with a long history of multiple symptomatic hyperkeratotic papules on the palms and soles. In addition, we review the literature and present the current classification of the heterogeneous group of punctate palmoplantar keratoses, the cutaneous and histologic findings, the differential diagnosis, the possible association with various anomalies including malignancies, and the various treatment options.

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Case Report

A 61-year-old German woman whose medical history was significant only for osteoarthritis presented with a long duration of multiple hyperkeratotic papules on the palms and soles. The patient recalled the palmar lesions first appeared at approximately age 15 years. She denied any history of arsenic exposure. Her occupations included gardening and working as a housewife. All cancer screenings appropriate for her age, including mammography, fecal occult blood testing, colonoscopy, and Pap test, were current; no malignancies have been detected to date. Family history revealed 6 other relatives spanning 4 generations with similar lesions on the hands and soles (Figure 1). All family members in the pedigree were generally healthy without any reported history of malignancies. On examination, the patient had multiple 2- to 3-mm discrete keratotic papules over the palmoplantar surfaces that were confluent in areas involving the weight-bearing surface of her soles (Figures 2 and 3). The patient described some tenderness in these areas when standing and walking. Histologically, the keratotic papules revealed a compact hyperkeratotic plug with a slight depression in the underlying epidermis (Figure 4). No parakeratosis or cornoid lamellae were present. The patient was initially treated with daily salicylic acid 40% and urea 40% cream with some improvement of the hyperkeratosis. At follow-up one month later, daily tazarotene 0.1% gel was added, which resulted in further improvement and resolution of the pain after 3 months.

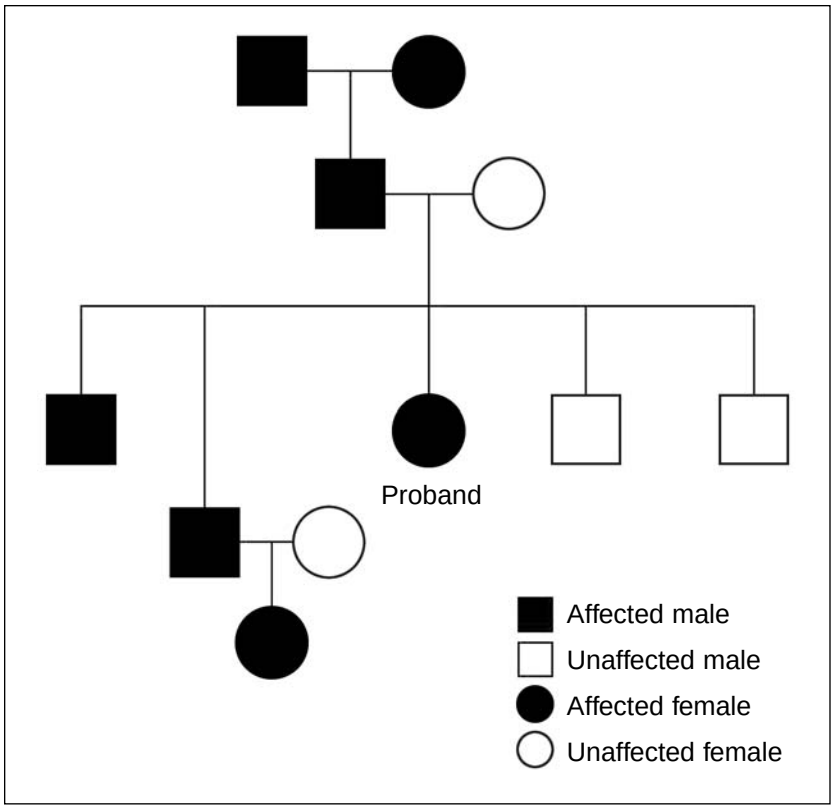

Figure 1. The patient's family pedigree shows those members affected with keratosis punctata palmoplantaris.

Comment

The first description of keratosis punctata palmoplantaris (KPPP) was reported by Buschke and Fischer[1] in 1910. Three years later, Brauer[2] reported a family with clinically similar lesions that appeared to be hereditary. The disorder is thus often referred to as Buschke-Fischer-Brauer disease. Various synonyms have been used to describe this genodermatoses (Table 1).[3-7]

Currently, the classification of palmoplantar keratodermas (PPKs) is based on clinical morphology, distribution of the lesions, histology, modes of inheritance, and, in some cases, molecular pathology.[3,8,9] The "simple" PPKs, which involve only the skin, can be divided into 3 types: diffuse, focal, and punctate. The punctate PPKs are subdivided into acquired and hereditary forms. Acquired forms include arsenical keratoses and keratosis punctata of the palmar creases. The hereditary forms of punctate PPKs include KPPP (type I punctate PPK, Buschke-Fischer-Brauer disease), spiny keratoderma (type II punctate PPK, porokeratosis punctata palmaris et plantaris), focal acral hyperkeratosis, and acrokeratoelastoidosis.[3,7,8]

KPPP is transmitted as an autosomal-dominant trait with variable penetrance.[6-9] The lesions of KPPP develop over the palmoplantar surface between the ages of 12 to 30 years, with a peak incidence in the second decade, as was the case in our patient. Most reports suggest predominance in black patients with a roughly equal sex ratio overall.[4-7] The incidence in one large series is reported as 1.17 per 100,000 people.[6] The primary lesions, which typically begin over the lateral edge of the digits, are slightly raised, sharply marginated, round to oval, skin-colored papules. The size of the lesions range between 2 to 20 mm. Over time and

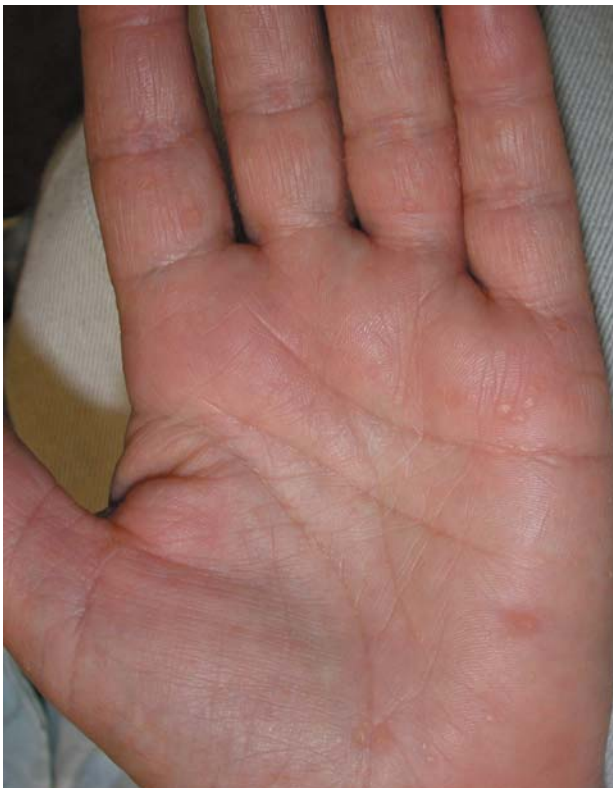

Figure 2. Numerous 2- to 3-mm discrete keratotic papules on the palm and fingers.

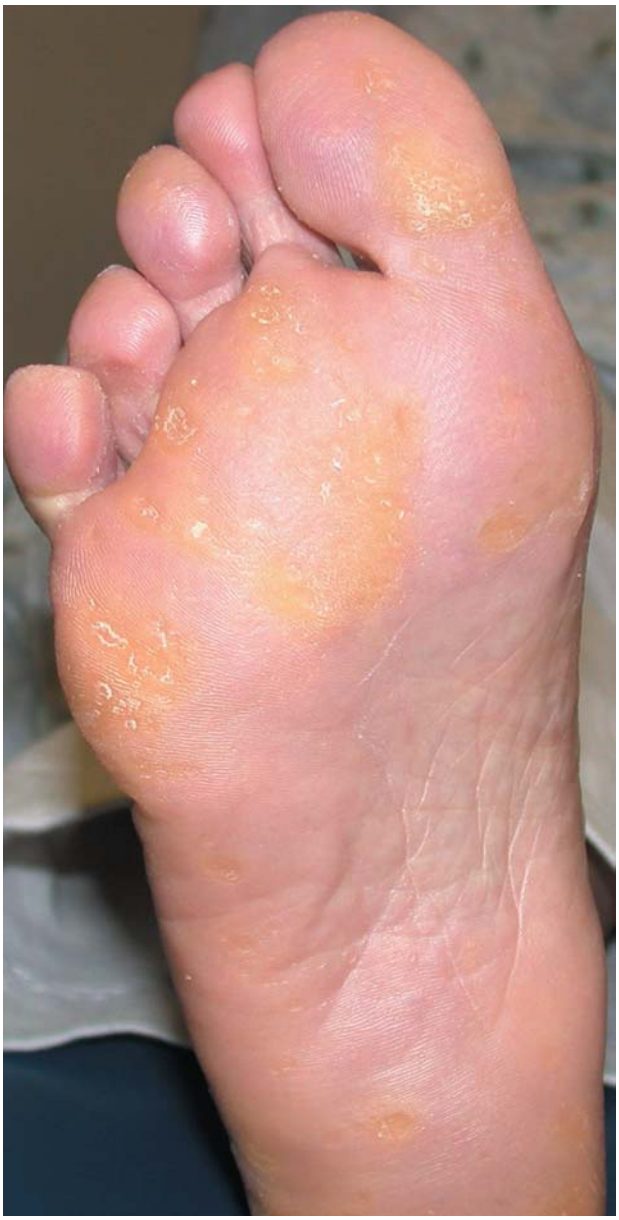

Figure 3. Numerous keratotic papules on the sole that are confluent in the weight-bearing areas.

with repetitive trauma, the hyperkeratotic lesions become enlarged, turn more yellow-brown, and distribute irregularly over the entire palmoplantar surface. The plantar lesions may coalesce into a more diffuse pattern over the pressure points. The number of lesions per person may range from 1 to more than 40 papules, with an average in one study of 8.3.[4] Removal of the deep central portion leaves a depression in which the original lesions will reform during a period of weeks. The lesions may be accentuated with immersion in water.[7]

Most patients with KPPP are asymptomatic and are often diagnosed incidentally on examination; however, in some cases, symptoms of burning, pruritus, and pain hindering daily activities, such as walking or manual labor, have been noted.[4] Hyperhidrosis is uncommon, but nail abnormalities such as longitudinal fissures, onychogryphosis, and onychomadesis are frequently reported.[4,10] The course of the disease is long-term, and spontaneous resolution has not been reported in the literature.

Histologic specimens from KPPP lesions reveal circumscribed compact columns of massive hyperkeratosis and a normal to mildly increased granular layer. There is usually a slight depression in the epidermis beneath the plug (Figure 4).[4]

The differential diagnosis of punctate keratoses of the palms and soles can be extensive (Table 2).[4,11-22] Following is a discussion of the clinical characteristics of the acquired and hereditary forms of primary punctate palmoplantar keratoses.

Arsenical keratoses are one of several cutaneous manifestations of long-term arsenic exposure. Sources of exposure to this toxic metal include well water, medicine, mining and smelting of various metals, and industrial pollution.[11-12] Drinking water contaminated with naturally high levels of inorganic arsenic is a significant problem in many parts of the world. For example, in Bangladesh and

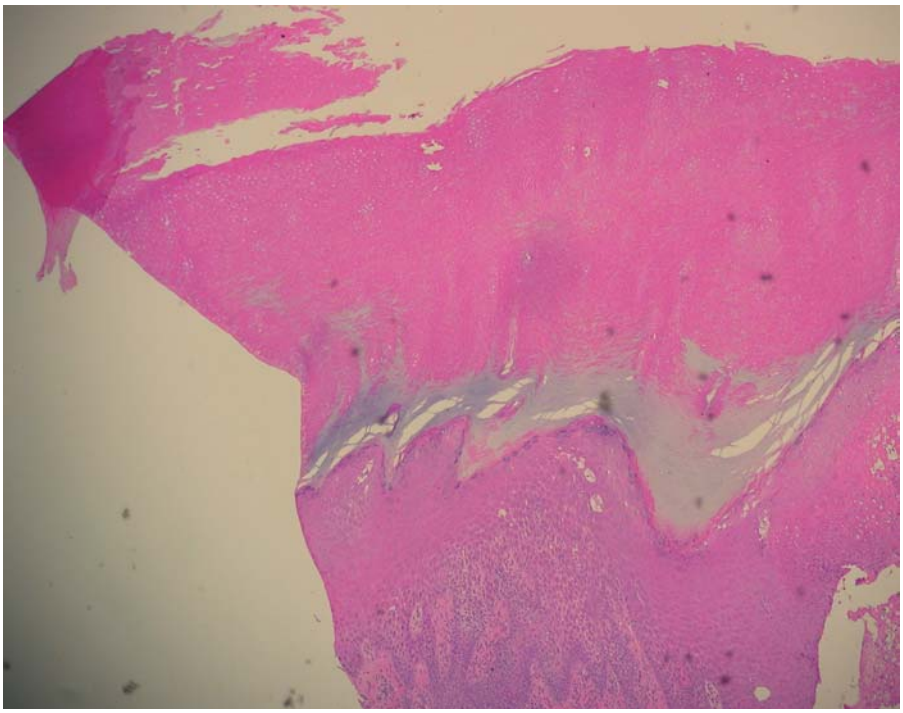

Figure 4. Biopsy results from the palm show a compact hyperkeratotic plug with a slight depression in the underlying epidermis (H&E, original magnification ×10).

West Bengal, India, an estimated 79.9 million and 42.7 million inhabitants, respectively, are exposed to groundwater arsenic concentrations that far exceed the World Health Organization maximum permissible limit of 50 μg/L.[12] In both of these populations, the primary source of drinking water is from tube wells, which draw water from underground aquifers contaminated with geological sources of arsenic.[12] Arsenical keratosis is characterized by hyperkeratotic papules that typically develop over the palms and soles. The lesions may appear anywhere between 4 to 30 years after exposure and may degenerate into squamous cell carcinoma or, more rarely, basal cell carcinoma.[11-13] A detailed history is thus warranted if arsenic exposure is suspected. Associations with internal malignancies, including hepatic angiosarcoma, bronchial adenocarcinoma, bladder cancer, and nonmelanoma skin cancer, have been reported.[11-14]

Table 1.

Synonyms Used to Describe Keratosis Punctata Palmoplantaris[3-7]

Buschke-Fischer-Brauer disease
Keratosis punctata
Keratoderma punctata
Keratosis papulosa
Papulotransluscent acrokeratoderma
Keratoderma punctatum and maculosa disseminata
Davis-Colley disease
Keratoma dissipatum hereditarium palmare et plantare
Keratoma disseminatum palmaris et plantaris
Keratodermia maculosa dissemintata symmetrica palmaris et plantaris
Keratodermia punctata hereditaria
Keratodermia palmoplantaris papulosa

Keratosis punctata of the palmar creases appears to be predominantly found in the Afro-Caribbean population, but the prevalence is unclear, varying from 1.5% to 69% in different series.[4,15-17] The lesions are characterized by discrete, translucent, keratotic papules primarily in the palmar creases of the hands. They are usually asymptomatic but may

Table 2.

Differential Diagnosis of Punctate Keratoses of the Palms and Soles

Verrucae vulgaris
Arsenical keratoses
Porokeratosis punctata
Spiny keratoderma
Cowden disease (multiple hamartoma syndrome)
Darier disease (keratosis follicularis)
Acrokeratoelastoidosis costa
Focal acral hyperkeratosis
Clavi

be painful. Many authors suggest this disease is related to manual labor. No associations with malignancy have been reported.[4,5,15-17]

Spiny keratoderma is an autosomal-dominant condition with an age of onset ranging from 12 to 59 years.[18-20] Clinical presentation is characterized by numerous tiny keratotic spines over the entire palmoplantar surfaces, resembling the spines of an old-fashioned music box.[18] Histologically, these spines correspond to columnar parakeratosis resembling cornoid lamellae. This finding is absent in the KPPP form. The term *spiny keratoderma* was coined by Osman et al[18] to distinguish this condition from porokeratosis, which is clinically and histologically a distinct entity. Confusion exists about whether or not the lesions of spiny keratoderma are a form of porokeratosis because previously designated names incorporated the term *porokeratosis*. The names *punctate porokeratotic keratoderma, porokeratosis punctata palmaris et plantaris,* and *punctate porokeratosis of the palms and soles* have been previously used to describe these spiny lesions.[18-20] The punctate variant of true porokeratosis is clinically characterized by discrete 1- to 2-mm seedlike hyperkeratotic plugs surrounded by a thin raised margin.[21-22] These lesions may be arranged linearly or may coalesce to form plaques, which are not observed with spiny keratoderma.[21] The histologic hallmark of porokeratosis is the cornoid lamella, which consists of a thin column of parakeratotic cells extending through the surrounding orthokeratotic stratum corneum, an absent granular layer below the column of parakeratosis, and vacuolated or dyskeratotic cells at the base. Proper classification is needed because malignant degeneration has been reported with certain variants of porokeratosis.[18,21]

Acrokeratoelastoidosis and focal acral hyperkeratosis are clinically similar entities and share an autosomal-dominant inheritance pattern. Clinical findings consist of 2- to 4-mm round to oval keratotic papules on the borders of the hands, feet, and wrists. The papules may be umbilicated in some cases and may become confluent in the center of the palms and soles. The lesions typically first develop in childhood or adolescence but may occur in adult life. Local hyperhidrosis may be present in acrokeratoelastoidosis but has not been reported for focal acral hyperkeratosis. These 2 entities are mainly distinguished histologically. Focal acral hyperkeratosis exhibits only hyperkeratosis, whereas acrokeratoelastoidosis has the additional finding of elastorrhexis. There have been no reported associations with malignancies.[3,23]

Keratotic palmoplantar papules also are cutaneous manifestations of multisystem disorders such as Darier disease and Cowden disease.[24-25] Patients with these disorders typically have a multitude of other mucocutaneous and systemic findings to support these diagnoses. Histologically, the keratotic lesions of Darier disease are similar to that of KPPP in that hyperkeratosis is found in both. However, Darier disease also demonstrates follicular plugging, parakeratosis, and irregular acanthosis with papillomatosis.[24] The keratotic lesions of Cowden disease show nonspecific orthokeratosis, hypergranulosis, and acanthosis.[25] A thorough examination, family history, and histologic evaluation are all necessary to make an accurate diagnosis.

Various anomalies and diseases such as corneal opacities, spastic paralysis, epilepsy, oligophrenia, colonic adenocarcinoma, and gastroduodenal ulcers have been reported infrequently in association with KPPP[8,10,26-34]; however, none were observed in our case.

As previously mentioned, KPPP is transmitted as an autosomal-dominant trait. The causative gene, however, has not been identified. Linkage to keratin gene clusters 12q and 17q has been excluded by Kelsell et al.[27] Various authors propose that the defect may lie in another gene involved in epithelial development and/or regulation in keratin expression (ie, genes responsible for structural proteins that are integral to keratin filament assembly and function).[7,8,10]

Unlike diffuse and focal PPKs, the association of punctate PPKs with malignancies is not well established. To date, only 3 reports of inherited punctate

PPK and malignancy have been published. Bennion and Patterson[33] reported a small kindred of 8 affected individuals; 2 developed adenocarcinoma of the colon and 1 developed adenocarcinoma of the pancreas. Interestingly, none of the family members without punctate keratoses developed cancer of any type. Ena et al[34] reported a family with 8 affected members, one of whom developed adenocarcinoma of the colon at 53 years of age. The statistical significance in these 2 studies is questionable due to the small number of subjects involved. Stevens et al[30] reported a larger kindred of more than 320 individuals spanning 4 generations. In this study, 10 of 43 adults with punctate PPK developed malignancies, including Hodgkin disease and renal, breast, pancreatic, and colon adenocarcinomas. Of the remaining 277 unaffected individuals, 6 developed malignancies.

Discovery of the causative gene(s) would serve at least 2 purposes: (1) it would provide insights into the possible association of punctate PPK and malignancy and (2) it may lead to an improved classification of the heterogeneous group of punctate PPKs.

Historically, KPPP was treated with mechanical debridement and topical keratolytics, which only provided temporary control. More recently, systemic retinoids have been used with improved results; however, relapse is reported with cessation of treatment. Baran and Juhlin[35] treated a patient with a disabling case of KPPP with etretinate 75 mg daily and observed significant clinical improvement after 3 weeks. The patient remained free from the hyperkeratoses with a maintenance dose of 50 mg daily; however, the lesions recurred when the dose was further decreased to 25 mg daily. Hesse et al[36] also treated a disabling case with acitretin, the active metabolite of etretinate, and observed similar success. Treatment with acitretin 30 mg daily resulted in significant, but incomplete, regression of the lesions after one month. Relapse occurred upon cessation of treatment; however, adequate control was maintained with 10 to 20 mg daily.

We chose to treat our patient with a trial of tazarotene 0.1% gel to minimize potential adverse reactions present with long-term use of oral retinoids. After 3 months of daily application of tazarotene, the hyperkeratotic lesions significantly diminished in size, and more importantly to the patient, the pain over the pressure areas resolved. Given our positive experience with tazarotene, topical retinoids may be a practical alternative for mild cases of KPPP. Long-term use is likely required for optimal control given the high relapse occurrence observed with cessation of oral retinoids.

Conclusion

In conclusion, we presented a case of KPPP in a patient with a strong family history supporting the autosomal-dominant inheritance pattern. The causative gene has not yet been identified, but its discovery would provide more insight into the possible association with malignancy and also may lead to an improved classification of the punctate PPKs. Punctate PPK has an extensive differential diagnosis and, if unrecognized, may be confused with common entities such as verrucae, leading to unnecessary frustration from multiple ineffective treatments. Multisystem conditions such as Darier disease and Cowden disease also must be considered when evaluating a patient with palmoplantar punctate keratoses. A full cutaneous examination, family history, and histologic evaluation are important components in making an accurate diagnosis. Treatment options include mechanical debridement, topical keratolytics, and topical and systemic retinoids. Maintenance therapy is required with all forms of treatment to prevent relapse.

REFERENCES

1. Buschke A, Fischer W. Keratodermia maculosa disseminata symmetrica palmaris and plantaris. *Ikonographia Dermatologica*. 1910;5:183-192.
2. Brauer A. Über eine besondere form des hereditären keratoms (keratoderma dissiminatum hereditarium palmare et plantare). *Arch Derm Syph (Berlin)*. 1913;114:211-236.
3. Lucker GPH, Van de Kerkof PCM, Steijlen PM. The hereditary palmoplantar keratoses: an updated review and classification. *Br J Dermatol*. 1994;131:1-14.
4. Rustad OJ, Vance JC. Punctate keratoses of the palms and soles and keratotic pits of the palmar creases. *J Am Acad Dermatol*. 1990;22:468-476.
5. Anderson WA, Elam MD, Lambert WC. Keratosis punctata and atopy. report of 31 cases with a prospective study of prevalence. *Arch Dermatol*. 1984;120:884-890.
6. Stanimirovic A, Kansky A, Basta-Juzbasic A, et al. Hereditary palmoplantar keratoderma, type papulosa, in Croatia. *J Am Acad Dermatol*. 1993;29:435-437.
7. Stevens HP, Kelsell DP, Bryant SP, et al. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. literature survey and proposed updated classification of the keratodermas. *Arch Dermatol*. 1996;132:640-651.
8. Ratnavel RC, Griffiths WA. The inherited palmoplantar keratodermas. *Br J Dermatol*. 1997;137:485-490.
9. Itin PH. Classification of autosomal dominant palmoplantar keratoderma: past-present-future. *Dermatology*. 1992;185:163-165.
10. Salamon T, Stolic V, Lazovic-Tepavac O, et al. Peculiar findings in a family with keratodermia palmo-plantaris papulosa Buschke-Fischer-Brauer. *Hum Genet*. 1982;60:314-319.

11. Maloney ME. Arsenic in dermatology. *Dermatol Surg*. 1996;22:301-304.
12. Ratnaike RN. Acute and chronic arsenic toxicity. *Postgrad Med J*. 2003;79:391-396.
13. Schwartz RA. Arsenic and the skin. *Int J Derm*. 1997;36:241-250.
14. Steinmaus C, Yuan Y, Bates MN, et al. Case-control study of bladder cancer and drinking water arsenic in the western United States. *Am J Epidemiol*. 2003;158:1193-1201.
15. Smith EB, Jetton RL. Punctate pits and keratoses of the palmar creases. *South Med J*. 1970;63:1291-1293.
16. Penas PF, Rios-Buceta L, Sanchez-Perez J, et al. Keratosis punctata of the palmar creases: case report and prevalence study in Caucasians. *Dermatology*. 1994;188:200-202.
17. Weiss RM, Rasmussen JE. Keratosis punctata of the palmar creases. *Arch Dermatol*. 1980;116:669-671.
18. Osman Y, Daly TJ, Don PC. Spiny keratoderma of the palms and soles. *J Am Acad Dermatol*. 1992;26:879-881.
19. Friedman SJ, Herman PS, Pittelkow MR. Punctate porokeratotic keratoderma [editorial]. *Arch Dermatol*. 1989;125:1432.
20. Lestringant GG, Berge T. Porokeratosis punctata palmaris et plantaris. *Arch Dermatol*. 1989;125:816-819.
21. Rahbari HR, Cordero AA, Mehregan AH. Punctate porokeratosis. a clinical variant of porokeratosis of mibelli. *J Cutan Pathol*. 1977;4:338-341.
22. Himmelstein R, Lynfield YL. Punctate porokeratosis. *Arch Dermatol*. 1984;120:263-264.
23. Dowd PM, Harman RRM, Black MM. Focal acral hyperkeratosis. *Br J Dermatol*. 1983;109:97-103.
24. Martin RW, Michel B, Bergfeld WF. Intraepidermal vesicular, bullous, and pustular dermatoses. In: Farmer ER, Hood AF, eds. *Pathology of the Skin*. 2nd ed. New York, NY: McGraw-Hill; 2000:221-247.
25. Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). *J Am Acad Dermatol*. 1983;8:686-696.
26. Powell FC, Venencie PY, Gordon H, et al. Keratoderma and spastic paralysis. *Br J Dermatol*. 1983;109:589-596.
27. Kelsell DP, Stevens HP, Ratnavel R, et al. Genetic linkage studies in non-epidermolytic palmoplantar keratoderma: evidence for heterogeneity. *Hum Mol Genet*. 1995;4:1021-1025.
28. Kimyai-Asadi A, Kotcher LB, Jih MH. The molecular basis of hereditary palmoplantar keratodermas. *J Am Acad Dermatol*. 2002;47:327-343.
29. Paller AS. The molecular bases for the palmoplantar keratodermas. *Pediatr Dermatol*. 1999;16:483-486.
30. Stevens HP, Kelsell DP, Leigh IM, et al. Punctate palmoplantar keratoderma and malignancy in a four-generation family. *Br J Dermatol*. 1996;134:720-726.
31. Howel-Evans W, McConnell RB, Clarke CA, et al. Carcinoma of the oesophagus with keratosis palmaris et plantaris (tylosis): a study of two families. *Q J Med*. 1958;27:413-429.
32. Blanchet-Bardon C, Nazzaro V, Chevrant-Breton J, et al. Hereditary epidermolytic palmoplantar keratoderma associated with breast and ovarian cancer in a large kindred. *Br J Dermatol*. 1987;117:363-370.
33. Bennion SD, Patterson JW. Keratosis punctata palmaris et plantaris and adenocarcinoma of the colon. a possible familial association of punctate keratoderma and gastrointestinal malignancy. *J Am Acad Dermatol*. 1984;10:587-591.
34. Ena P, Cottoni F, Cerimele D, et al. Associazione della cheratodermia palmo-plantare punctata con altre condizioni morbose (canizie precoce, carcinoma del colon). G *Ital Dermatol Venereol*. 1986;121:45-54.
35. Baran R, Juhlin L. Keratodermia palmoplantare papuloverrucoides progressiva: successful treatment with etretinate. *J Am Acad Dermatol*. 1983;8:700-702.
36. Hesse S, Berbis P, Privat Y. Keratodermia palmo-plantaris papulosa (Buschke-Fischer's disease): efficacy of acitretin. *Br J Dermatol*. 1993;128:104-105.