Porokeratosis: a review of unique group of keratinizing disorder

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Abstract
Porokeratosis is a group of disorder of uncertain cause characterized by abnormal epidermal keratinization with the histologic finding of cornoid lamella. To date, five major clinical variants have been identified. This unique group of disorders of keratinization is reviewed here, with special reference to the differentiation of each component and their management.

Key words
Porokeratosis, porokeratosis of Mibelli, disseminated superficial actinic porokeratosis, porokeratosis palmaris et plantaris disseminate, linear porokeratosis, punctate porokeratosis, cornoid lamella.

Introduction
Porokeratosis is a clonal disorder of keratinization characterized by one or more atrophic patches surrounded by a clinically and histologically distinctive ridge-like border called the cornoid lamella. Five clinical variants of porokeratosis are recognized: (i) classic porokeratosis of Mibelli (PM), (ii) disseminated superficial actinic porokeratosis (DSAP), (iii) porokeratosis palmaris et plantaris disseminate (PPPD), (iv) linear porokeratosis (LP), and (v) punctate porokeratosis (PP). Porokeratosis most commonly occurs in fair-skinned individuals and is relatively rare in darker-skinned races. PM and PPPD affect men twice as often as women. DSAP is three times more common in women compared with men and LP is seen with equal incidence in both sexes. PPPD and LP may be seen at any age, from birth to adulthood, PM usually develops in childhood, DSAP generally develops in the third or fourth decade of life. Lesions may be found anywhere, including the mucous membranes, although they most commonly occur on the extremities. A verrucous variant that is localized to the buttocks and resembles psoriasis has been reported in several patients. Several risk factors for the development of porokeratosis have been identified; these include genetic inheritance, ultraviolet radiation, and immunosuppression. Excessive natural or artificial ultraviolet radiation, electron beam therapy, and extensive radiation therapy are well-established trigger factors. Immunosuppression may induce new lesions or cause preexisting lesions to flare.

The approach to treatment is individualized, based on the size of the lesion and the anatomical location, the functional and aesthetic considerations, the risk of malignancy, and the patient’s preference. Protection from the sun, use of emollients, and watchful observation for
signs of malignant degeneration may be all that is needed for many patients. Various medical and surgical modalities are also available. Excision is most appropriate when malignant degeneration develops. Cryotherapy, electrodesiccation and curettage are minimally invasive methods of inducing resolution for large numbers of lesions. Diamond fraise dermabrasion and laser therapy has also been used with conflicting reports of efficacy. The prognosis is generally excellent. Patients who develop PM or linear porokeratosis because of immunosuppression are at higher risk for the development of a squamous or basal cell carcinoma within the lesion. Linear porokeratosis is associated with a higher risk of malignant degeneration.\(^{17-19}\) PM circumferentially involving the digits may induce pseudoainhum.\(^{20}\) Patients must practice strict sun precautions and must periodically examine their skin for lesions suggestive of malignancy.

**Historical Background**

Porokeratosis was first described by Mibelli\(^1\) in 1893 as one or more localized, chronically progressive, hypertrophic irregular plaques with central atrophy and a prominent peripheral ridge. A more superficial disseminated form was described independently almost at the same time by Respighi\(^2\) and later by Andrews.\(^23\) A linear variant was added early in the last century.\(^24\) Disseminated superficial actinic porokeratosis\(^25\) was described in 1966 and porokeratosis palmaris et plantaris disseminate\(^26\) was added to the spectrum in 1971.

**Etiology and Pathogenesis**

The exact etiology of the various types of porokeratosis is unknown. An autosomal dominant mode of inheritance has been reasonably well established for PM,\(^27,28\) PPPD,\(^26\) DSP, and DSAP.\(^29\) Linear porokeratosis has been observed in monozygotic twins.\(^30\) The similarities of clinical appearance and histopathology as well as the coexistence of different variants of porokeratosis in one patient or in several members of an affected family make a strong case for considering them different phenotypic expressions of a common genetic aberration.\(^31,32\) Risk factors for porokeratosis include genetic inheritance, ultraviolet light exposure, and immunosuppression. One study found that approximately 10% of patients who had undergone renal transplantation developed porokeratosis.\(^1,7-10\) An autosomal dominant mode of inheritance has been established for familial cases of almost all forms.

**Classic porokeratosis (Mibelli)** Autosomal dominant inheritance and immunosuppression are the usual causes.\(^27,28\) PM has also been seen following radiation therapy, at burn wounds, and at hemodialysis sites.\(^33\)

**Disseminated superficial (actinic) porokeratosis** Sun exposure and/or artificial ultraviolet radiation exposure in a patient who is genetically predisposed cause DSAP. Exacerbations have been reported following prolonged sun exposure, repeated tanning bed exposure, electron beam radiation therapy, and therapeutic phototherapy or photochemotherapy for psoriasis. Drug-induced photosensitivity may play a role. Protection from ultraviolet radiation may lead to spontaneous resolution. Immunosuppression predisposes patients to both DSAP and nonactinic DSP.\(^36\) Because of this, a viral etiology has been hypothesized.
**Linear porokeratosis** No definite inheritance pattern has been established. Loss of heterozygosity has been proposed as a genetic mechanism and may explain the higher risk of malignant degeneration seen in linear porokeratosis in comparison to other forms of porokeratosis. 30,37

**Porokeratosis palmaris et plantaris disseminate** Familial PPPD is transmitted in an autosomal dominant mode with variable penetrance. 26 Acquired PPPD may be caused by immunosuppression, or it may be a cutaneous marker of internal malignancy. 38

**Punctate porokeratosis** This condition has no unique inheritance pattern and is usually associated with other forms of porokeratosis. 39

Clinical Variants

1. **Porokeratosis of Mibelli** [Figure 1]
   It generally starts in childhood as a small, asymptomatic or slightly pruritic lesion that expand over a period of years, but may develop during adulthood and enlarge rapidly, usually in the clinical setting of immunosuppression. Occasionally, patients have a history of an antecedent trauma, such as a burn wound. The lesion develops as a small, light brown, keratotic papule that slowly expands to form an irregularly shaped, annular plaque with a raised, ridgelike border. This border may be hypertrophic or verrucous and is usually greater than 1 mm in height. A thin furrow is typically seen in the center of the ridge, causing a Great Wall of China effect. The lesion is slightly hypopigmented or hyperpigmented, minimally scaly, slightly atrophic, hairless, and anhidrotic. The size may vary from a few millimeters to several centimeters. Lesions may be found anywhere, including the mucous membranes, although they most commonly occur on the extremities. 1,3,4,6,27,28,33

2. **Disseminated superficial (actinic) porokeratosis** [Figure 2]
   Multiple, brown, annular, keratotic lesions that develop predominantly on the extensor surfaces of the legs and the arms characterize DSAP. They are usually asymptomatic, but they may itch slightly. Facial lesions are seen in approximately 15% of patients, and the face may be the only area of involvement. Patients are typically women in their third or fourth decade of life, with a history of excessive ultraviolet exposure. Patients may have a history of phototherapy for psoriasis. 1,8,19,31,34,35

3. **Non-actinic disseminated superficial porokeratosis**
   Non-actinic forms may be seen following electron beam total skin irradiation, organ transplantation, hepatitis C virus related hepatocellular carcinoma, HIV infection, renal failure, or in association with other causes of immunosuppression. Dozens of small, indistinct, light brown patches with a threadlike border are seen on the extensor surfaces of the arms and the legs. Non actinic DSP may have a generalized distribution, sparing the palms and the soles. 34,40-42

4. **Linear porokeratosis** [Figure 3]
   During infancy or early childhood, a unilateral, linear array of papules and plaques with the characteristic raised peripheral ridge are seen unilaterally on an extremity, the trunk, and/or the head and neck area. The lesions commonly follow a dermatomal distribution. Multiple linear groups may be seen in one patient, typically on the same side. They may be seen in
Individual lesions within the linear grouping have a well-developed border, often with a central furrow similar to that seen in classic PM. Clinical changes consistent with the development of a basal or squamous cell carcinoma are more common in linear porokeratosis than in other forms of porokeratosis.\textsuperscript{1,17,24,30,37}

\textbf{Figure 1} Porokeratosis of Mibelli over central face of an elderly person.

\textbf{Figure 2} Disseminated superficial actinic porokeratosis over forearm.

\textbf{Figure 3} Linear porokeratosis over hand.

\textbf{Figure 4} Porokeratosis palmaris plantaris et disseminate lesions over planter region.

\textbf{Figure 5} Porokeratosis palmaris plantaris et disseminate lesions over calf region.
5. Porokeratosis palmaris et plantaris disseminate [Figures 4, 5]

Small, relatively uniform lesions are first seen on the palms and the soles, and then they develop in a generalized distribution, including the mucosal membranes. The lesions may itch or sting, but they are usually asymptomatic. The onset is typically during adolescence or early adulthood, and males are affected twice as often as females. The lesions are small and superficial with a slightly hyperpigmented, atrophic center and a minimally raised peripheral ridge. Mucosal lesions are small, annular or serpiginous, and pale. Squamous cell carcinoma has been reported to develop within lesions of PPPD.1,26,38,43,44

6. Punctate porokeratosis

Multiple, asymptomatic, tiny, seed-like, hyperkeratotic papules with thin, raised margins develop on the palms and the soles during adulthood. Patients usually have other forms of porokeratosis as well, most commonly the linear or Mibelli types. Punctate porokeratosis may be clinically and histologically indistinguishable from punctate porokeratotic keratoderma, which may be a cutaneous sign of an internal malignancy.39,45,46

7. Verrucous/hyperkeratotic variant

A verrucous variant that is localized to the buttocks and resembles psoriasis has been reported in several patients. Several cases of hyperkeratotic variants of PM and DSAP have also bee described.47,48

8. Giant porokeratosis

Rarely the lesions of porokeratosis may be 10-20 cm in diameter and the surrounding wall raised 1 cm. Mostly found on the foot and are said to have a high incidence of malignant transformation.32,49

9. Bullous porokeratosis

This has been described in association with disseminated superficial porokeratosis.50

10. Pruriginous porokeratosis

This variant has again been described in association with disseminated superficial porokeratosis.50,51

11. Zosteriform porokeratosis

Porokeratotic lesions have rarely been seen in dermatomal pattern.52

12. Mutilating variant

Mutilating and destructive lesions have been reported in PM.53,54

13. Malignant porokeratosis

Any porokeratosis developing fatal malignancies may be regarded as malignant porokeratosis.55

Association with cutaneous malignancies

The exact molecular mechanism of carcinogenesis developing in various forms of porokeratosis remains unclear, but chromosomal instability and reduced immune surveillance with over expression of p53 are hypothesized to play a role in the development of cutaneous malignancies within porokeratosis. Sudden aggravation of DSP and DSAP should prompt a search for an underlying disease causing immunosuppression. Squamous cell carcinoma, Bowen's disease and basal cell epithelioma have been observed and are more likely in large isolated lesions of PM, but malignant transsformation has also been observed in DSP and DSAP and linear porokeratosis. Widespread metastases and fatal outcome have rarely been reported.1,2,7,19,56-60
Histopathology [Figure 6, 7]

Porokeratoses are grouped because of their histologic hallmark, the cornoid lamella, and the resulting clinical features. It has been proposed that, in porokeratosis, a mutant clone of epidermal cells expands peripherally, leading to formation of a cornoid lamella at the boundary between the clonal population and normal keratinocytes and represents the pathologic substrate for the ridge-like border. The cornoid lamella arises in the interfollicular epidermis and may involve the ostia of hair follicles or sweat ducts, which have led to the misnomer porokeratosis. It consists of a tightly packed, thin column of parakeratotic cells extending through the entire thickness of the surrounding orthokeratotic stratum corneum. It occupies an indentation of the epidermis that is generally tilted away from the center of the lesion. The adjacent epidermis is hyperkeratotic and acanthotic to a variable degree. The granular layer is missing below the cornoid lamella, and single or clustered dyskeratotic cells and vacuolated keratinocytes are found at its base. The papillary dermis beneath the cornoid lamella contains a moderately dense inflammatory infiltrate and dilated capillaries. The center of the lesion is usually atrophic, with areas of liquefactive degeneration in the basal layer, colloid body formation, and flattening of rete ridges, whereas the dermis may be edematous or fibrotic with telangiectasia. In essence, similar histopathologic changes are encountered in all forms of porokeratosis. However, in DSP, DSAP and PPPD, the cornoid lamella is less pronounced or so minimal as to be difficult to recognize.1,21,60,61

Diagnosis and differential diagnosis

Diagnosis of porokeratosis is usually made with ease, both clinically and histopathologically. The continuous keratotic ridge cleaved by a longitudinal furrow, which surrounds the lesions both in the Mibelli type and the other variants, is quite diagnostic, as is the localization and distribution of lesions. Elastosis perforans serpiginosa can be similar to PM, but it consists of erythematous, keratotic papules and lacks the continuous ridge with its furrow. The superficial, disseminated types of porokeratosis may resemble actinic keratoses, stucco keratoses, flat seborrheic keratoses, or flat warts. Small, discrete lesions may be mistaken for lichen sclerosus et atrophicus, lichen planus, acrokeratosis verruciformis, and pityriasis rubra pilaris, but each of these others lacks the fine, slightly raised, threadlike border. Neoplastic
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disorders, such as cutaneous T cell lymphoma (CTCL), can mimic lesions DSAP or PM clinically. Histologically, the lesions lack a cornoid lamella and reveal infiltrates typical of CTCL. Punctate porokeratosis should be differentiated from punctate keratoderma and planter warts.1,6,62,63

Treatment

The optimal treatment modality must be selected depending on the lesion's size and localization, functional and aesthetic requirements, and the general condition of the patient. The lesion can recur with any therapeutic modality. Lubrication usually improves the symptoms in superficial forms of porokeratosis, as does keratolytic treatment of hyperkeratotic lesions. Topical 5 fluorouracil is highly effective in PM, linear porokeratosis, and in DSP and DSAP. Treatment must be continued until a brisk inflammatory reaction is obtained that seems to be a prerequisite for clearing and can occur as a delayed reaction. The use of oral retinoids has yielded conflicting results: whereas excellent results were obtained in some patients with DSAP, widespread PM, PPPD and linear porokeratosis, one must be aware that relapses usually follow several weeks or months after discontinuation of retinoid therapy. It has been pointed out that retinoids might have an inhibitory effect on cutaneous carcinogenesis in porokeratotic lesions. Circumscribed lesions of PM or linear porokeratosis may be excised and grafted or destroyed by cryotherapy, electrodessication, dermabrasion, or CO₂ laser. All therapeutic measures that might increase the malignant potential of porokeratosis such as irradiation, immunosuppression, and excessive UV exposure should be avoided.11-16

Course and Prognosis

Prognosis is generally excellent in patients having no underlying immunosuppression and paucity of risk factors. Lesions may increase in size and number with time; while this may be an extremely slow process in PM, progression can be quite pronounced in DSP and particularly in DSAP after UV exposure. In immunocompromised patients, spontaneous fluctuations in severity and spontaneous remissions depending on the immune status have been described. Sudden aggravation of DSP and DSAP should prompt a search for an underlying disease causing immunosuppression. Malignant degeneration has been observed and is more likely in large isolated lesions of PM, but it has also been observed in DSP and DSAP and linear porokeratosis. Widespread metastases and fatal outcome have been reported. Several cases of giant PM in an acral location causing destruction of underlying soft tissue and bone and mutilation have been observed.17-20,53-55,64-66

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**Editor’s note**

From the next issue of JPAD, the ‘QUIZ’ section will be replaced by ‘PHOTODERMDIAGNOSIS’ section and it will be edited by Dr. Amor Khachemoune, MD. The manuscripts should be submitted to:

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