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Porokeratosis of Mibelli

Overview and Review of the Literature

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Porokeratosis of Mibelli is an uncommon dermatosis, which may be associated with immunosuppression and may undergo malignant transformation. Due to the wide range of clinical presentations, numerous classifications have evolved, resulting in some confusion. This article examines the classification and presentation of porokeratosis and, in particular, reviews the association with immunosuppression.

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Although porokeratosis (PK) was described more than a century ago, the disease continues to fascinate dermatologists, pathologists and oncologists alike. The disease has a unique clinical appearance, an obscure etiology, and frequently an unpredictable outcome.

PK is an uncommon disorder of the skin, characterized by one or more annular plaques with a surrounding raised horny border which spreads centrifugally. Since the first description of the disease, many additional variants of PK have been described, each with differing morphological shapes, distribution and clinical course. Furthermore, an association with cutaneous epithelial malignancies as well as immunosuppression has been noted. This review examines the wide clinical spectrum of PK, its histology, and its associations.

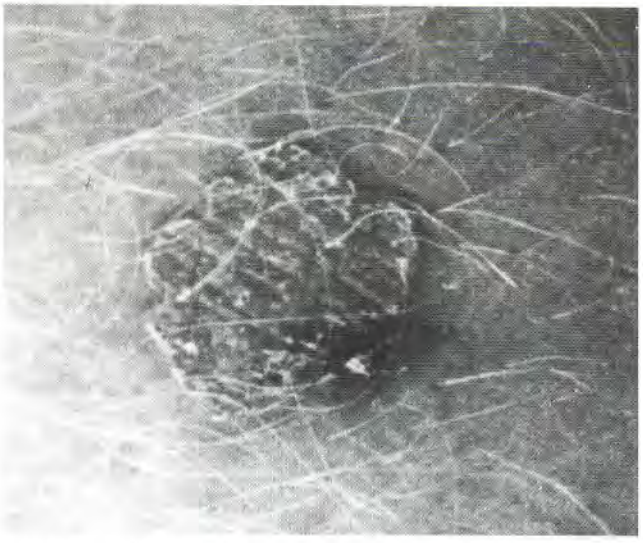

Fig. 1. Typical lesion of porokeratosis, showing raised keratotic rim and atrophic, scaly, central region.

HISTORICAL ASPECTS AND CLASSIFICATION

In 1893, Mibelli (1) described a male in which lesions of varying size and form had been present on the arms and hands since the age of 2. In his introductory note, however, Mibelli acknowledged that a similar condition had, in fact, been observed and published by Respighi a year earlier under the title "Eccentric Hyperkeratosis". In Mibelli's patient, the lesions were whitish-red and were bordered by an elevated, uninterrupted ridge. The patient's father, brother and sister were similarly affected. Believing the condition to be hyperkeratosis involving the pores of sweat ducts, Mibelli mis-termed the lesions "porokeratosis", and the disease subsequently became known as "Porokeratosis of Mibelli" (PM). Literature frequently refers to this disorder as the "classic" or "plaque" form of PM. Two variants of classic PM were subsequently described: a linear form of porokeratosis of Mibelli (LPM) has been widely attributed to Truffi (2), although it should be noted that Mibelli's original case description seems to be that of LPM. A punctate form of porokeratosis of Mibelli (PPM) was described by Rahbari et al. (3) in 1977.

In 1893, quite independently from Mibelli, Respighi (4) described a disseminated and more superficial form of porokeratosis, but the term disseminated superficial porokeratosis (DSP) was only introduced in 1937 by Andrews (5). Two variants of DSP were subsequently described. In 1966, Chernosky (6) described a form of DSP that was present mainly on sun-exposed areas and was exacerbated by sun exposure. He termed the condition disseminated superficial actinic porokeratosis (DSAP). A second variant of DSP was described in 1971 by Guss et al. (7), in which initial palmar and plantar involvement was followed by dissemination. This variant has been termed porokeratosis plantaris, palmaris et disseminata (PPPD).

Malignant degeneration in lesions of PK was first reported by Vigne (8) in 1942, and the tendency of immune-suppressed individuals to develop PK was noted by MacMillan & Roberts (9) in 1974.

In addition to the aforementioned varieties, a bewildering number of morphological forms, such as facial PK (10), giant PK (11), and punched-out PK (12), have been reported, resulting in several differing classifications. To avoid ambiguity, PK may be considered to comprise only two prime forms: localized and disseminated, each of which has three clinical presentations (Table I).

Reticulated PK (13), a disorder occurring on non-sun-exposed areas, malignant disseminated PK (14), a widespread eruption not related to sun-exposure in which squamous and basal cell carcinomas develop, as well as eruptive pruritic papular PK (15) may all be considered to be forms of DSP. Giant PK (16) and zosteriform PK (17, 18) may be included in PM and LPM, respectively. Some reports of punctate keratoderma (19) are probably mis-diagnosed variants of

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Table I. *Classification of porokeratosis (PK)*

Porokeratosis type	Abbreviation
Localized forms	
Classic or plaque-type porokeratosis of Mibelli	PM
Linear porokeratosis of Mibelli	LPM
Punctate porokeratosis of Mibelli	PPM
Disseminated forms	
Disseminated superficial porokeratosis	DSP
Disseminated superficial actinic porokeratosis	DSAP
Porokeratosis plantaris palmaris et disseminata	PPPD
Immunosuppression-induced porokeratosis	ISIP

PPM, since they exhibit the histological hallmark of PK, i.e. cornoid lamella. Porokeratotic eccrine and dermal duct nevus is a dermatosis that follows the lines of Blaschko (20–22). Although it may be a distinct entity, it is probably a form of LPM. Porokeratosis punctata palmaris et plantaris (23, 24) and punctate porokeratotic keratoderma (25, 26) are probably the same disease entity. Despite the author's statement that it is not a true form of PK, a cornoid lamella is nevertheless present, and the condition may thus be considered to be a form of PPM. Porokeratosis plantaris discreta (27, 28) has little clinical resemblance to the other forms of PK and, despite its name, is probably a plantar clavus. It is non-familial, appears in adulthood on pressure-bearing areas, and comprises a single keratotic horn that does not spread centrifugally. Histological examination does not show the presence of a cornoid lamella.

ETIOLOGY

PK is believed by many to be a geno-dermatosis. An autosomal dominant mode of inheritance with partial penetrance has been reported for PM (29, 30) PPM (19, 25), DSP (31), DSAP (32), as well as PPPD (7). However, many reported sporadic cases are probably the result of somatic mutations (33). Further evidence of a geno-dermatosis is that cultured fibroblasts derived from porokeratotic lesions exhibit instability of the short arm of chromosome 3, as well as numerous re-arrangements and clone formation (34, 35). Despite the many morphological forms of PK, it has been suggested (36) that the similar histology as well as the co-existence of different variants within a single patient or within different members of an affected family (37) are different phenotypic expressions of a common genetic disorder. Alternatively, PK may be due to the simultaneous expression of two closely linked gene loci.

It is believed that the epidermis comprises several genetically determined clones of cells (38). In PK, however, it has been postulated that some of these clones are inherited as mutants whose phenotypic expression is the result of activation by external trigger factors (39, 40). Several such trigger factors have been suggested:

a) Irradiation

Sunlight exposure clearly plays a clear role in the induction of DSAP – a disorder confined to sun-exposed skin, and in which exacerbations are often experienced during the summer months (41). PUVA therapy (42, 43) and light therapy (44) have also been implicated in the induction of the disease, and dermal fibroblasts derived from porokeratotic skin have been shown to be hypersensitive to X-irradiation (45). A single case report has linked PK to therapy with thiazides, drugs which are known to be potential photosensitizers (46). It should be noted, however, that the relative scarcity of facial lesions in DSAP (10, 47), the histopathological absence of actinic changes in PK, the development of DSAP in black patients (48, 49), as well as a single report in which PK lesions actually improved after PUVA therapy (50), question the exact role of irradiation in the etiology of DSAP.

b) Infective agents

An infective agent was first suspected in 1932, when a specimen of porokeratotic skin injected into the sub-cutaneous abdominal skin of a guinea-pig resulted in inflammatory and epidermal changes similar to those seen in PK (51). An infective etiology was also postulated in two immunosuppressed patients who had multiple systemic infections and developed PK (52). In a patient who developed PK after a kidney transplant, it was pointed out that the donor kidney could conceivably carry a quiescent virus which could have been activated by immunosuppressive therapy (9). The authors noted that the apparent dominant mode of inheritance could be explained if such a virus were capable of vertical transmission and further suggested that a mutant epidermal clone may be triggered by activation of a latent virus, as has been described for actinic keratoses and spino-cellular tumors developing in patients with renal transplants (53). In a patient with chronic PK who developed an IgA immune-complex glomerulo-nephritis, it was suggested that released bacterial antigens from the PK lesions may have initiated this unusual form of glomerulo-nephritis (54). Auto-inoculation (41) and a repeated attempt at animal inoculation, however, have failed to replicate the initial guinea-pig findings, and electron microscopy as well as tissue-culture techniques have thus far failed to demonstrate the presence of any viral particles (41).

c) Trauma

The isomorphic (Koebner) phenomenon has been demonstrated in classic PM (55, 56), as well as in LPM (57). PK has also developed in a burn, suggesting that dermal injury may be an initiating factor (58). The Koebner phenomenon has not, however, been described in other variants of PK, and deliberate attempts to induce the phenomenon in DSAP have proved unsuccessful (41).

d) Immunosuppression

Immunosuppression-induced porokeratosis (ISIP) is a relatively new disease entity and is thus examined in detail below.

A search of the literature has revealed at least 40 cases of ISIP (9, 52, 59–74). The male to female ratio was 8:3, and the age varied from 19 to 70 years (mean 48 years). Immunosuppression was administered for a variety of conditions, including transplantation (heart, kidney, liver, marrow), liver disease (chronic active hepatitis, biliary cirrhosis), acute myelomonocytic leukemia, and skin disorders (hidradenitis suppurativa, pemphigus foliaceus and vulgaris, mycosis fungoides, and systemic lupus erythematosus). The immunosuppressive therapy included methyl-prednisolone, azathioprine, cytosine-

Table II. *Features of porokeratosis*

	PM	LPM	PPM	DSP	DSAP	PPPD
Age of onset	Childhood	All ages	Childhood	10–30 years	20–40 years	Teens or twenties
Inheritance	Autosomal dominant	?	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant
Male: female	2–3:1	1:1	?	?	1:1	2:1
Palms & soles	+	+	+	±	−	+
Pruritus	No	No	No	±	±	±
Sites	Anywhere	Limbs	Palms & soles	Generalized	Sun-exposed skin later generalized	Palms/soles
No. of lesions	Solitary or few	Few to many	Multiple	Multiple	Hundreds	Tens to hundreds
Malignant degeneration	Reported	Reported	?	Reported	Rare	Reported
ISIP	+	+	?	+	+	?
Cornoid lamella	Prominent	Prominent	Prominent	Prominent	Poorly developed	Poorly developed
Mucosal involvement	±	−	−	−	−	±
Koebner phenomenon	+	+	−	−	−	−

For abbreviations see Table. 1

arabinoside, cyclophosphamide, hydralazine, daunorubicin and cyclosporin A. The latency period between start of immunosuppressive therapy and the onset of ISIP varied from 1 week to 16 years. In the majority of cases, the porokeratosis developed on the legs or arms, but involvement of the chest, buttocks and back was also noted. Many authors failed to specify the exact variety of PK, but the disseminated form occurred in about 50% of cases. In one case, pre-existing PK was exacerbated by immunosuppressive therapy (9).

PK has also been reported in a patient with two associated autoimmune diseases, namely active chronic hepatitis and vitiligo (75). It has also been described in a patient with cystic fibrosis, where overstimulation of the immune system from secondary bacterial infections may result in immunosuppression (76).

Several postulates regarding PK and immunosuppression have been put forward. It has been suggested that the mutant clones of epidermal cells are held in check either by adjacent normal epidermal cells or by classic immune mechanisms (9). Either of these mechanisms may be impaired by immunosuppressive therapy, leading to the development or exacerbation of ISIP. A further suggestion is that previous UV irradiation induces a latent skin change, which is subsequently stimulated by immunosuppressive therapy (52). This would account for the large number of DSAP cases. Immunosuppression and sunlight exposure have both been shown to decrease the density and to impair the function of epidermal Langerhans' cells in human renal allograft recipients (77). In an immuno-histochemistry study of ISIP lesions, defects in the expression of HLA-DR antigens by epidermal Langerhans' cells were demonstrated (74). The authors postulated that immunosuppression causes a failure of Langerhans' cell immunosurveillance and the consequent proliferation of the abnormal clone of keratinocytes.

CLINICAL MANIFESTATIONS

a) Porokeratosis of Mibelli (PM)

Although PM can appear at any age, onset is usually during childhood. In non-hereditary cases, however, the age of onset is usually later. It is two to three times more common in males than in females. The true incidence of PM remains undetermined. About 36% of all published cases of PK involve PM (78), but this is probably a gross over-estimation of the actual incidence, since many case reports do not specify the exact type of PK.

The lesions of PM may be solitary or a few and are usually confined to the extremities. Palms and soles may be involved. Lesions have been reported to occur on the face, glans penis and on the oral mucosa (79). Reports of corneal or conjunctival involvement (80, 81), however, may be questioned as there have been no reports of such lesions in recent medical literature. Giant forms of PM are commoner on the feet. The lesion begins with asymptomatic papules, which slowly enlarge in a centrifugal fashion, leaving the central portion hairless, slightly atrophic and hypopigmented. Occasionally, the central area may be hyperpigmented or hypertrophic. The raised border can be as high as 1 cm in giant forms of the disease and has a typical "dike" at the apex. A radial cross-section through the border would thus be "M"-shaped. The mature

lesion may be rounded, serpiginous or annular. The isomorphic phenomenon may occur.

b) Linear porokeratosis of Mibelli (LPM)

This form of PK usually appears in childhood but may occur in middle life. Although the isomorphic phenomenon may occur in LPM, linear lesions arise independently. LPM is believed by some to be a nevoid aberration (82). The lesions present as linear, zosteriform, or elongated arcuate patterns, primarily involving the extremities. Unilateral lesions frequently occur and are often mis-diagnosed as linear epidermal nevi, linear psoriasis, lichen striatus, lichen planus, or even mosaic plantar warts (83).

c) Punctate porokeratosis of Mibelli (PPM)

This is inherited in an autosomal dominant fashion, but one reported pedigree affected only males (23). A congenital, unilateral form of PPM has been described in a female (84). A further variant has been described, in which the lesions resembled the tiny spines, or spokes, of old-fashioned musical boxes (23). The lesions consist of multiple, discrete, seed-like lesions which are surrounded by a thin raised border. The lesions may coalesce to form plaques. They occur primarily on the soles or palms. The differential diagnosis for this type of lesion includes nevoid basal-cell carcinoma syndrome, arsenical keratoses, Darier's disease, pitted keratolysis and palmo-plantar lichen nitidus. Punctate or papular forms of keratoderma may look similar to PPM, but the histology reveals hyperkeratosis rather than the typical cornoid lamella seen in PK.

d) Disseminated superficial porokeratosis (DSP)

DSP is a disseminated form of PK occurring on both sun-exposed and non-exposed areas. An autosomal dominant mode of inheritance is likely. The arms, neck, trunk and face are commonly involved. The age of onset is usually during the first three decades of life (85). The lesions are not prominent and may have the clinical appearance of atrophic lichen planus. A case of DSP associated with dermal amyloidosis has been reported, in which some of the lesions were annular and lichenoid (86). Pruritus may be a feature.

e) Disseminated superficial actinic porokeratosis (DSAP)

DSAP has the same morphological features as DSP but is limited to light-exposed skin. It is the commonest clinical type of PK. It affects both sexes equally, but females are more likely to seek medical advice. It usually appears during the third and fourth decades of life (47). Lesions range in number from tens to several hundreds. The lesions begin as small papules which are often follicular in location. The papules enlarge centrifugally over months or years, leaving a central atrophic area and a fine keratotic rim. The lesions of DSAP are far less prominent than in classic PM and may thus be overlooked. Indeed, in one study, 8 out of 29 patients were totally unaware of their condition until pointed out at the time of examination (47). Even the clinician may have difficulty in visualizing the rim without the aid of optical magnification. The lesions are confined to sun-exposed areas, with the arms, legs, shoulders and back being particularly affected. Paradoxically, and unlike DSP, involvement of the face is rare. The palms, soles and mucosal surfaces are spared. Pruritus is a common symptom, especially after heat or sun-exposure. DSAP often shows seasonal fluctuations with exacerbations typically occurring during the summer months. Lesions can be artificially induced by exposure to ultraviolet light (43). Notably, the condition has been reported to occur in black patients (48, 87).

f) Porokeratosis palmaris plantaris et disseminata (PPPD)

PPPD is characterized by the development of keratotic papules, initially confined to the palms and soles, but later developing elsewhere (7). The lesions usually appear in the teens or early twenties. Numerous, superficial papular lesions initially develop on the palms and soles. They are red to brown in color and enlarge centrifugally over several months. The mature lesion is from 4 to 5 cm in diameter. The peripheral ridge does not have the central "dike". The process is usually bilateral and symmetrical. After months or years, a secondary, more generalized, eruption develops, particularly on the extremities and on the anterior and posterior trunk. The mucosa may be affected (88). An unusual presentation may involve initial disseminated lesions, followed by subsequent palmar and plantar involvement (89). Both sun-exposed as well as unexposed skin can be involved. The disseminated lesions may be pruritic, and 25% of patients report an exacerbation of the lesions during summer.

HISTOPATHOLOGY

Despite the wide variety of morphological forms of PK, the histopathological features are remarkably uniform and similar. The pathological hallmark of PK is the "cornoid lamella", typically found at the border of the lesion. The cornoid lamella forms an indentation within the epidermis, the apex of which typically points away from the center of the lesion. It comprises a column of parakeratosis extending through the orthokeratotic stratum corneum. It is frequently seen arising in the ostia of involved hair follicles, although it is now generally accepted that the cornoid lamella is not related to the sweat gland. The cornoid lamella stains more deeply with keratin stains than keratin in the central portion of the lesion or in normal skin. The cornoid lamella is poorly developed in lesions of DSAP and PPPD. Although the cornoid lamella is a constant and diagnostic criterion in PK, it has been noted to occur in several other conditions including basal cell carcinoma, squamous cell carcinoma *in situ*, solar keratoses, milia, verrucae, scar tissue, seborrheic keratoses and in solitary inflammatory conditions (90). The granular layer beneath the cornoid lamella is usually absent or markedly reduced in thickness. Loose clusters of dyskeratotic cells and/or vacuolated cells may occasionally be seen in the spinous layer beneath the cornoid lamella. These dyskeratotic cells are believed to be the abnormal epidermal clones. The papillary dermis underlying the cornoid lamella often shows the presence of a moderate lympho-histiocytic infiltrate. The tissue directly beneath the cornoid lamella stains PAS positive but is diastase-sensitive, presumably due to the presence of glycogen. The epidermis in the central portion of the lesion may be normal, thin, hyper-keratotic, or occasionally acanthotic. Liquefaction degeneration of the epidermal-dermal

interface may also be present (91). Ultrastructural studies in DSAP have revealed re-duplication of the basal lamina at the dermo-epidermal junction and degraded organelles within the parakeratotic cells of the cornoid lamella.

POROKERATOSIS AND SKIN MALIGNANCIES

A recent review of malignant transformation in porokeratotic lesions revealed at least 56 published cases (78). The malignancies included Bowen's disease of the skin, as well as squamous cell and basal cell carcinomas. Many patients developed multiple tumors (39%). The review noted that approximately 11% of all PK cases will undergo malignant transformation, but others report the incidence of malignant transformation as 7.5% (92) and 6.8% (93). Due to publication bias, however, these figures are probably an over-estimation of the true incidence. The review indicated that malignant lesions were more frequent on non-exposed skin, in large PK lesions, and in those patients who had previous ionizing radiation exposure. The average latency period was 36 years but was shorter in PM and longer in LPM. It has been noted (94) that those PK patients developing malignancy had a longer disease duration (33.5 years vs. 13.7 years) than PK patients without cutaneous malignancy. Malignant transformation was described in all varieties of PK but was most common in LPM and rare in DSAP. Metastatic disease, including fatal cases, has been reported (95, 96). Pre-malignant changes have been found in epidermal cells of PK lesions. Using microfluorometric methods to measure the DNA content of epidermal cells in PK lesions, DNA polyploidism was found in 42% of PK lesions. An increased proportion of cells in the S-phase and/or G_2M-phase of the cell cycle was also found. The DNA histographic distribution pattern for PK was shown to be intermediate between Bowen's disease of the skin and normal control skin (97). A similar study has shown that small solitary lesions had less epidermal ploidy abnormalities than larger, coalesced lesions (98).

It has also been shown that keratinocytes from the center of PK lesions exhibit identical staining patterns to those observed in other pre-malignant lesions, such as actinic keratoses. Furthermore, keratinocytes beneath the cornoid lamella have a staining pattern similar to that observed in squamous cell carcinomas, whereas keratinocytes peripheral to the cornoid lamella show a normal staining pattern (99).

It seems unlikely that UV radiation plays a significant role in inducing malignant transformation, since such transformation is rare in DSAP, and most reported malignancies have occurred in areas not exposed to the sun. Furthermore, histologic changes due to actinic damage were only rarely found in association with the lesions.

TREATMENT

The therapeutic response of all forms of PK remains poor. General measures, such as lubrication and the use of keratolytics, may improve the symptoms but do little in the way of treating the actual lesion. Topical sunscreens should be prescribed in patients with DSAP. Localized lesions may be removed by surgical excision, cryotherapy with liquid nitrogen, CO_2 laser (100) or dermabrasion (101). Isolated reports have noted varying responses to treatment with topical or intralesional cortisone (41), topical hydrocortisone (52), topical 5-fluorouracil (7, 41, 102) and topical tretinoin (103). Systemic etretinate seems to offer the best therapeutic response (43, 104–106), but recurrence following cessation of therapy (107), as well as a case report noting exacerbation of lesions due to etretinate therapy (108), serve to temper enthusiasm for the drug. One report has noted a dramatic response to systemic corticosteroid therapy (109).

Despite numerous case reports and studies, an adequate form of treatment for PK remains elusive. Furthermore, the initial hypothesis that PK is due to an abnormal clone of epidermal cells remains unproven. These points, together with the wide spectrum of clinical presentations, and the association with malignancy and immunosuppression, provide a challenge, not only to the dermatologist, but to pathologists and oncologists alike.

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