Porokeratosis: An enigma beginning to unravel

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Abstract

Porokeratosis is a keratinization disorder with unclear etiopathogenesis, varied clinical presentation and characteristic histopathology, and is usually unresponsive to current therapeutic options. Until now, it was considered to be a clonal disorder with immunity, ultra violet radiation and other factors playing important roles in etiopathogenesis. It is now known that abnormalities in the mevalonate pathway are responsible for this clonal keratinization abnormality. New variants of porokeratosis like eruptive bullous, pruriginous, lichen planus like, follicular variants and porokeratoma have been described. While the cornoid lamella is the classical histopathologic feature, dermoscopy and reflectance confocal microscopy make the diagnosis clearer. Development of malignancy in a few variants is a concern. Linear, disseminated superficial actinic and giant lesions are most prone to developing malignancies. Bowen's disease, squamous cell carcinoma, basal cell carcinoma and even melanoma have been reported in cases of long-standing porokeratosis. Newer modalities of therapy such as photodynamic therapy, ingenol mebutate and HMGCoA inhibitors may play a role in the future.

Key words: Cornoid lamella, malignancy, mevalonate kinase, porokeratosis

Introduction

Porokeratosis is an enigmatic skin condition in terms of its etiopathogenesis, clinical presentation, histopathology and treatment options. Considered as a clonal keratinizing disorder of uncertain etiology,[1] it clinically manifests as solitary or multiple atrophic patches surrounded by a hyperkeratotic ridge-like border which histopathologically corresponds to the cornoidlamella.[2] A comprehensive English language literature search was done for porokeratosis across multiple databases (PubMed, EMBASE, MEDLINE and Cochrane) for keywords (alone and in combination). MeSH as well as nonMeSH terms such as "porokeratosis," "history," "classification," "pathogenesis," "clinical variants," "histology," "cornoid lamellae," "dermoscopy" and "treatment" were taken into consideration, for the purpose of this narrative review.

Porokeratosis was first described by Neumann in 1875.[3] However, the naming of the condition is attributed to Mibelli, an Italian dermatologist, who coined the term "porokeratosis" because of the involvement of eccrine ostia in his patient.[4] A superficial disseminated form of porokeratosis was described by Respighi in 1893[5] and Andrews in 1937.[6] The linear variant was described by Truffi in 1905.[7] The lesions of disseminated superficial actinic porokeratosis were described by Chernosky and Freeman in 1966.[8] Porokeratosis palmaris et plantaris disseminata was added to the spectrum in 1971.[9]

Porokeratosis is slightly commoner in males.[10] The lesions may be found anywhere on the body (most commonly extremities), though mucosal involvement is very rare.[11]

Classification

Porokeratosis is mainly classified into localized and generalized forms. Common localized variants are classical porokeratosis of Mibelli, linear porokeratosis, punctate porokeratosis, solar facial porokeratosis and genital porokeratosis.[12,13] Generalized variants are disseminated superficial porokeratosis, disseminated superficial actinic porokeratosis and disseminated palmoplantar porokeratosis. Unusual variants include hyperkeratotic porokeratosis, pruritic popular porokeratosis, verrucous porokeratosis (localized to buttocks)[14] and reticulate porokeratosis. A simplified classification is presented in Table 1.

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Table 1: Classification of porokeratosis

1. Localized
a. Porokeratosis of Mibelli
b.Genital porokeratosis (ptychotropica)
· Classical
· Hyperkeratotic
· Ptychotropica (classical)
· Ulceroproliferative
· Verrucous
· Penoscrotal
c. Linear porokeratosis
d. Zosteriform porokeratosis
e. Punctate porokeratosis
f. Giant porokeratosis
g. Solar facial porokeratosis
h. Reticulate porokeratosis
2. Generalized
a. Disseminated superficial actinic porokeratosis
b. Disseminated superficial porokeratosis
c. Eruptive bullous disseminated porokeratosis
d. Pruriginous porokeratosis
e. Follicular porokeratosis
f. Porokeratosis palmaris et plantaris disseminativa
3. Porokeratosis-like conditions
a. Porokeratotic eccrine ostial and dermal ductal nevus
b. Porokeratoma
c. Porokeratotic lichen planus

Pathogenesis

Previously, it was assumed that cornoid lamellae emerge from sweat pores, but it was eventually understood that this concept was not correct. Ultraviolet light exposure, electron beam therapy, extensive radiation therapy, immunosuppression, transplant procedures, immunodeficiency syndromes, chronic renal failure, chronic liver disease, infections, hematological malignancies including lymphomas, HIV infection and hepatitis C virus infection have all been implicated in the pathogenesis.[15-25] Drugs such as etanercept and adalimumab have also been implicated.

Local and systemic immunosuppression leading to reduction of immune surveillance and dysregulated proliferation of abnormal keratinocyte clones has been a well- accepted theory. There was also growing evidence of upregulation of genes involved in wound healing, epidermal differentiation (S100 calcium-binding protein) and regulation of T-cell-mediated immune responses, especially in disseminated superficial actinic porokeratosis.[26]

Abnormal keratinocyte apoptosis was a proposed pathogenic factor in porokeratosis. This was best exemplified again in disseminated superficial actinic porokeratosis, which showed the presence of TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) - positive apoptotic cells seen under the conical lamellar structure. Abnormal apoptosis leading to abnormal loricrin expression affecting terminal keratinocyte differentiation and finally to dyskeratosis was another favored theory of pathogenesis.[27]

It is now understood that abnormalities in the mevalonate pathway are responsible for the pathogenesis of porokeratosis. Abnormalities in the genes *MVD* (mevalonate decarboxylase), mevalonate kinase, *PMVK* (phosphomevalonate kinase), *FDPS* (farnesyl diphosphate synthase) and solute carrier family 17 member 9 (*SLC17A9*) have been found to be pathogenic in porokeratosis.[28] To date, at least 173 variations in mevalonate kinase, 14 variations in mevalonate decarboxylase, seven variations in phosphor mevalonate kinase and seven variations in farnesyl diphosphate synthase have been associated with porokeratosis. The complex mevalonate pathway is required for generation of isoprenoids, dolichol, ubiquinone, isopentenyl adenine and farnesyl pyrophosphate. These are key intermediate products required for cholesterol and sterol biosynthesis. They also act as ligands for hormone and growth receptors. Since cholesterol forms an important constituent of the cell membrane and affects many processes such as anti-inflammatory and oxidative stress reactions, epidermal differentiation and migration of cells, variations in the mevalonate pathway affect cholesterol and steroid biosynthesis and thereby result in abnormal differentiation of keratinocytes leading to the disease.[29]

Disseminated superficial actinic porokeratosis is described as an autosomal dominant disease with five loss-of-function mutations identified on linkage analysis: 12q23·2-q24·1,12q24·1-q24·2,15q25·1-q26·1,1p31·3-q31·1and16q24·1-q24·3.[30] Mitochondrial dysfunction induced by mevalonate kinase (MVK) mutations may be an important contributory mechanism in disseminated superficial actinic porokeratosis pathogenesis, since mevalonate kinase may have a protective effect on apoptosis of keratinocytes induced by ultraviolet-A spectrum light. The familial inheritance of disseminated superficial actinic porokeratosis has also been associated with mutations in SSH1, ARPC3 and SART3 genes. Disseminated superficial actinic porokeratosis is also considered a benign intraepidermal neoplastic process and is one of the genetic tumor disorders explained by Knudson's two-hit hypothesis.

Segmental disseminated superficial actinic porokeratosis[31] is believed to develop in a background of genetic alterations of keratinocytes in early embryogenesis leading to altered activity of regulatory proteins.[32] Linear porokeratosis has been observed in monozygotic twins.[33]

Variants such as verrucous porokeratosis, genital porokeratosis and pruritic papular porokeratosis are precipitated by friction, scratching, long-term compression, partial moisture and chronic skin disease. Burns and infections have also been proposed as inciting factors in porokeratosis.[34,35]

Bullous changes in porokeratosis are attributed to underlying edema and localized extravasation of interstitial fluid. Morgan *et al*. postulated that abnormal keratinocytes are

unable to provide adequate intercellular junctions, leading to such extravasation.[36]

Clinical features of individual variants

Porokeratosis of mibelli

This classical variant is characterized by solitary plaques with a thread-like hyperkeratotic margin [Figure 1], most commonly located on the extremities.[37] Other sites of involvement include the face, genitalia and trunk. Lesions are usually asymptomatic and persistent, though uncommonly they may resolve spontaneously.

Disseminated superficial actinic porokeratosis

Currently considered the most common variant of porokeratoses worldwide, this is an autosomal dominant dermatosis, presenting with asymptomatic, bilaterally symmetrical and disseminated brown, annular, keratotic lesions, most commonly distributed over the sun-exposed extensor surface so flower extremities, arms and face in middle-aged women [Figure 2].[38] The axillae, groins, perianal region, palms, soles and mucous membranes are spared. Lesions have atrophic centre and are surrounded by thin, elevated and furrowed, palpable keratotic rim. Sun exposure is a prominent etiological factor.

Disseminated superficial porokeratosis

The lesions here look similar to those in disseminated superficial actinic porokeratosis, but photo-distribution is not noted in disseminated superficial porokeratosis. Risk factors for the development of disseminated superficial porokeratosis include electron beam irradiation, organ transplantation, hepatitis C virus–associated hepatocellular carcinoma, HIV infection, renal failure and other causes of immunosuppression.

Bullous eruptive disseminated porokeratosis

Disseminated superficial actinic porokeratosis and disseminated superficial porokeratosis are often included under "eruptive disseminated porokeratosis," which is characterized by an acute onset and generalized distribution.[39] Secondary bullous changes in eruptive disseminated porokeratosis has been seen, though rarely.[36,40] An underlying neoplastic process may be found in few cases.

Pruriginous porokeratosis

This is another rare type of porokeratosis, which has been described in association with disseminated superficial porokeratosis.[41] Earlier called eruptive popular pruritic porokeratosis, it manifests as suddenly appearing itchy lesions which then heal in a few months with post-inflammatory hyperpigmentation.

Genital porokeratosis

The first case of porokeratosis localized to the genitalia was described by Helfman and Poulos.[42] Since then, numerous cases have been reported, and this is now proposed to be a distinct clinical entity.[43,44] Lesions start as erythematous papules which progress to plaques, nodules or ulcers.[45,46] Various presentations of genital porokeratosis have been observed:[47,48]

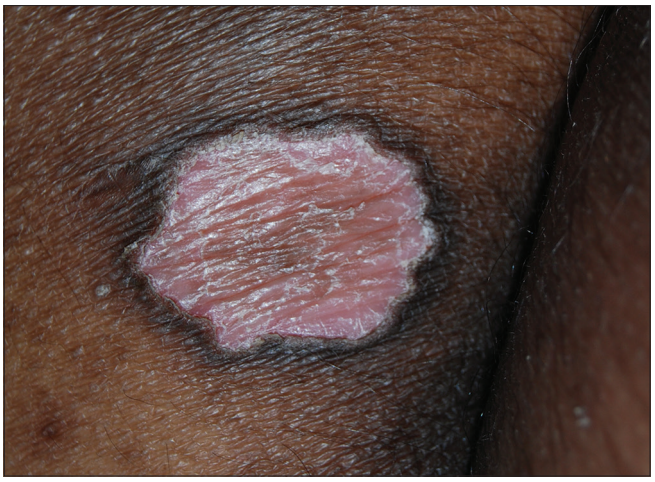

Figure 1: Classical solitary plaque of porokeratosis of Mibelli with central atrophy and peripheral keratoticrim

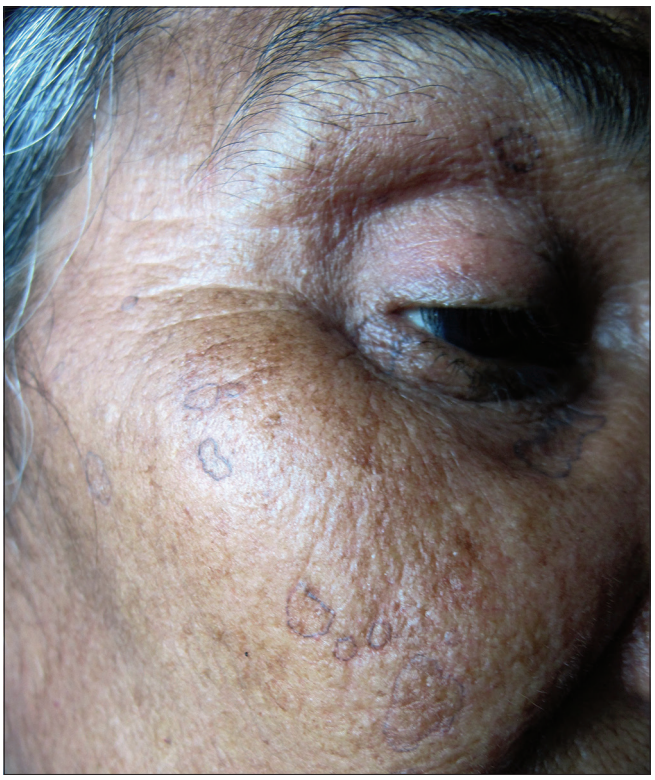

Figure 2: Disseminated superficial actinic porokeratosis on the face

- Classical porokeratosis of Mibelli-like: round atrophic patches with an elevated rim, located over the penis, scrotum and pubic region[49-51]
- Hyperkeratotic variant: plaques with a thickened central region and a raised hyperkeratotic margin, located over the perianal region and buttocks
- Porokeratosis ptychotropica: presenting with butterfly-shaped plaques and verrucous hyperplasia, usually seen on the buttocks [Figure 3].[52-58] Satellite lesions in the periphery may sometimes be noted. Anal mucosa is not affected. Lucker *et al*., in 1995 coined the term

"porokeratosis ptychotropica" (Greek word *ptyche* meaning fold and trope meaning turning, to emphasize the flexural location).[59] Other terms for this condition include verrucous porokeratosis, hyperkeratotic porokeratosis, follicular porokeratosis and genitogluteal porokeratosis. Stone *et al*. came across a similar condition, but it was associated with pruritus and they coined the term "perianal inflammatory verrucous porokeratosis."[60] This rare condition has mostly been seen in adults.

- Ulceroproliferative variant: round ulcerated plaques, over the penis and scrotum.[61]
- Verrucous variant: keratotic and hypertrophic plaques and nodules in the genito-crural region[14]
- Penoscrotal variant: typically seen in young men in their third decade of life. Patients present with severely pruritic plaques and patches with a rough granular surface, distributed over the shaft of penis and anterior scrotum.[62]

The genital variant occurs mainly in middle aged males, often with severe pruritus. Diagnosis is usually delayed due to atypical location and morphology.

The current consensus is that all genital porokeratosis can be grouped under a single entity named porokeratosis ptychotropica and all the genital types described as variants thereof. No etiological risk factor for this variant has been identified, unlike the others. Malignant transformation also usually does not occur.

Linear porokeratosis

In this variant, the lesions of porokeratosis are distributed in a linear fashion (may or may not be blaschkoid). During infancy or early childhood, linear arrangement of papules and plaques with the typical elevated peripheral ridge may be observed unilaterally on limbs usually and rarely on trunk, head and/or neck [Figure 4]. The lesions usually follow a dermatomal distribution.[63-68] Loss of heterozygosity has been proposed as the pathomechanism and this could be responsible for the higher chances of malignant transformation.[69] No inheritance is, however, reported. The incidence of malignancy reported with this variant is as high as 20%.

Zosteriform porokeratosis

In rare situations, lesions of porokeratosis may be seen to develop along a dermatome.[70]

Punctate porokeratosis

The variant is typified by the development of numerous asymptomatic, minute, hyperkeratotic papules within, raised margins distributed over the palms and soles [Figures 5 and 6]. Patients may have other variants of porokeratosis (classical type and linear), in association with punctate porokeratosis.

Porokeratosis palmaris et plantaris disseminata

Initially, the lesions are small papules with a hyperpigmented, atrophic centres and elevated peripheral ridges distributed over the palms and soles. Eventually, the lesions spread to involve the entire body, including the mucosae. Adolescent males are the most commonly affected. This variant of

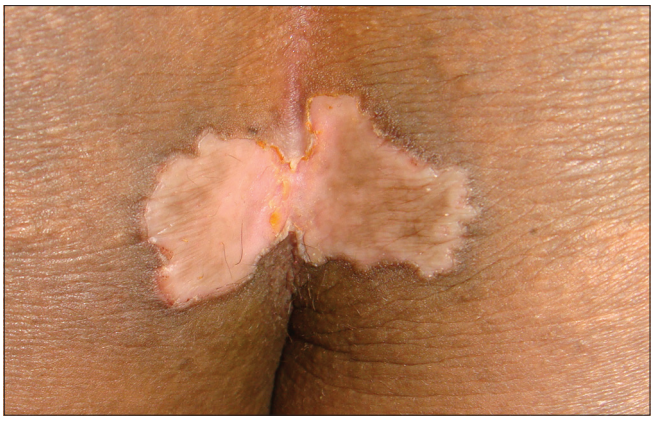

Figure 3: Classic butterfly lesion of porokeratosis ptychotropica

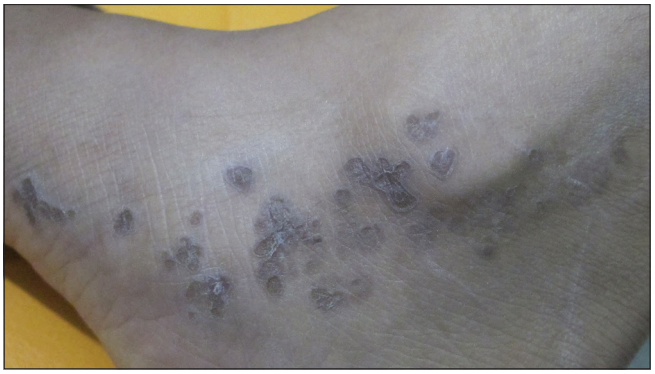

Figure 4: Linear porokeratosis on the foot and ankle

porokeratosis too has been reported to undergo malignant transformation.[71-73]

Giant porokeratosis

Rarely, the lesions of porokeratosis may enlarge to attain a dimension of 10–20 cm diameter, with the surrounding margin being elevated beyond 1 cm. These lesions have a high propensity to undergo malignant transformation.[74,75]

Porokeratotic eccrine ostial and dermal ductal nevus

It is an uncommon benign nevoid disorder characterized by the development to f histological features of porokeratosis. It is considered to be an eccrine hamartoma, presenting at birth or early childhood with multiple punctate or keratotic papules distributed over the extremities. Involvement of the palms and soles is characteristically observed and lesions are often systematized.[76-81]

Porokeratoma

Also known as porokeratotic acanthoma, it is a tumor-like acanthoma with features of porokeratosis (cornoid lamellation), commonly found on extremities, head and neck, chest and buttocks. It needs to be differentiated from porokeratosis of Mibelli. Clinically, it presents with scaly plaques, nodules with central hyperkeratosis and verrucous plaques. On histology, porokeratomas lack central epidermal atrophy (unlike porokeratosis) and cornoid lamellae are present throughout the stratum corneum instead of only at the borders (as in classical porokeratosis).[82-86]

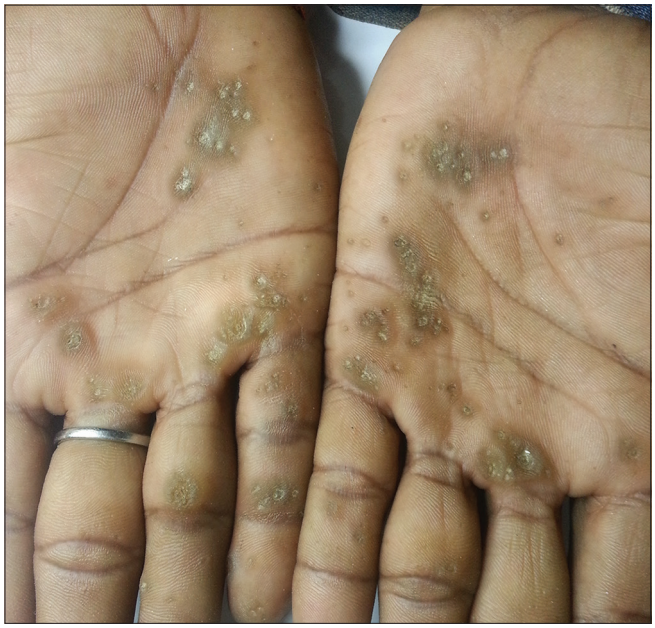

Figure 5: Punctate porokeratosis of palms

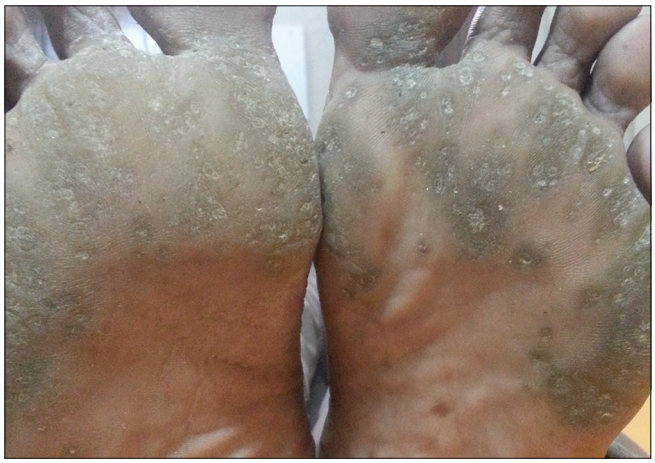

Figure 6: Punctate porokeratosis of soles

Porokeratotic lichen planus

This is a rare variant of porokeratosis, where in clinical and histopathological features of both conditions (lichen planus and porokeratosis) are present together.[87]

Follicular porokeratosis

This variety presents with erythematous to brown papules with the surrounding keratotic ridge. Itching is mild and not always present. Dyskeratosis extending into the follicular infundibulum is the hallmark on histopathology.[88]

Facial solar porokeratosis

Presentation with a few lesions on nasal and para nasal areas are described in this variant.

Reticulate porokeratosis

A reticulate variant, especially in the groins, has been reported.

Koebnerization and lichenification have also been reported in some variants[89] Rarely more than one type of porokeratosis may co-exist in a patient.

Dermoscopy

Dermoscopy of porokeratotic lesions reveals central brownish discoloration along with blue-gray dots, surrounded by a single hypopigmented band and a peripheral "white track."[90] Central scarring and enlarged capillaries are seen. Dermoscopy demonstrates iodine absorption by the cornoid lamella after polyvinyl-pyrrolidone-iodine application on the skin. The furrow ink test makes the ridge and rim more prominent. UV dermoscopy reveals a 'diamond neck lace' appearance at the borders.

Histopathology

The histologic hallmark is the presence of cornoid lamella, which is a tightly packed thin column of parakeratotic cells overlying a zone of focal hypogranulosis. It was regarded by Wade and Ackerman as a microscopic reaction pattern in 1980. It is an important diagnostic criterion that consists of a sloping column of parakeratosis associated with loss of the granular layer and underlying vacuolated keratinocytes, within a diffusely thin epidermis [Figure 7]. Lymphocytic inflammation of variable density, usually located in the papillary dermis, represents another reproducible finding. One may observe the presence of dyskeratotic keratinocytes below the spinous layer.[91] The papillary dermis beneath the cornoid lamella contains a moderately dense inflammatory infiltrate and dilated capillaries. The cornoid lamella sometimes focally extends into the hair follicles and intra epidermal eccrine sweat gland ducts.

Cornoid lamellae are usually solitary and located on one side of the clinical lesion in biopsies of classical porokeratosis of Mibelli. However, multiple cornoid lamellae have been observed in porokeratoma, penoscrotal porokeratosis and porokeratosis ptychotropica. They may develop around the adnexae (follicular infundibula and eccrine ostia) in porokeratotic eccrine ostial and dermal duct nevi. The presence of cornoid lamellae in the absence of classical clinical features of porokeratosis has been suggested to be an epidermal reaction pattern, which could be steroid-responsive or a forme fruste of longstanding disease.[92,93] Rarely, dermal amyloid deposits may be noted in cases of verrucous porokeratosis in underlying tuberculosis cases.[94]

Viral warts, actinic keratoses and some ichthyoses like ichthyosis hystrix may also show cornoid lamellae on histology.[95] Psoriasis vulgaris, dermatomyositis (Wong type), atypical keratosis lichenoides chronica (atypical Nekam's disease), pachyonychia congenita, verrucous epidermal nevus, squamous and basal cell carcinoma scan rarely show cornoid lamellae. All of these conditions can be considered as histological mimickers of porokeratosis.

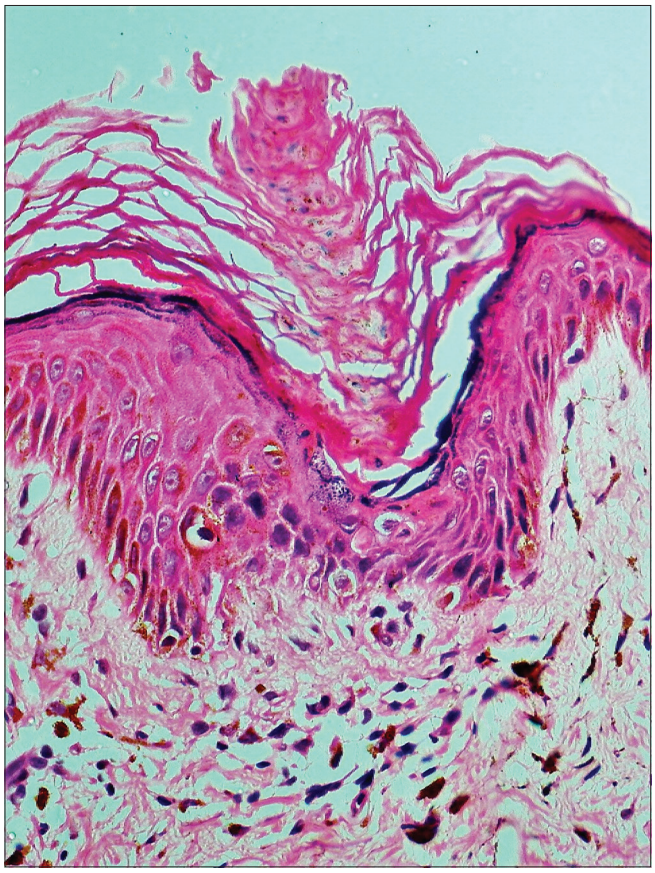

Figure 7: Cornoid lamella on histopathology. H&E stain: × 400

Reflectance photo microscopy can also be used as a mode of diagnosis. It is found to correlate well with horizontal biopsy and dermoscopic findings. Architectural disarray with loss of normal "honeycomb" pattern is seen in the center of the lesion, while in the periphery, less refractile destructured areas containing more refractile amorphous substance correlating with cornoid lamella is present.

Differential Diagnosis

The classical type is usually too typical in its appearance to be mistaken for some other entity. However, minute lesions of porokeratosis may be confused with actinic keratoses, stucco keratoses, verruca plana, lichen sclerosus et atrophicus, lichen planus and acrokeratosis verruciformis.

Differential diagnosis of disseminated superficial actinic porokeratosis includes guttate psoriasis, actinic keratosis, tinea corporis and pityriasis rosea.

The diagnosis of genitocrural porokeratosis is difficult and it closely mimics inverse psoriasis, tuberculosis verrucose cutis, viral warts, verrucous lichen planus, lichen simplex chronicus, lichen sclerosus, dermatophytosis, candidiasis, secondary syphilis, acrodermatitis enteropathica, epidermal nevus, Hailey-Hailey disease, Darier disease and extramammary Paget disease.

Punctate porokeratosis should be differentiated from punctate keratoderma and plantar warts. Porokeratotic eccrine ostial and dermal ductal nevus is usually confused with nevus comedonicus, linear verrucous epidermal nevus, inflammatory linear verrucous epidermal nevus (ILVEN), linear psoriasis, linear porokeratosis, dilated pore nevus, linear lichen planus, punctate palmoplantar keratoderma and punctate porokeratosis. Histopathology helps in differentiating the differentials from each other.

Complications

Long standing cases of porokeratosis may undergo malignant transformation (Bowen disease, squamous cell carcinoma, basal cell carcinoma and melanoma). Other complications include ulceration, soft-tissue destruction, disfigurement,[96] pseudoainhum with amputation and development of cutaneous horn.[74,97]

Transformation to malignancies

Premalignant lesions such as Bowen disease, cutaneous horns and dysplasia may develop in longstanding cases of porokeratosis, eventually progressing toward malignancy.[98-103] Squamous cell carcinomas may develop in 7.5–11% cases of longstanding porokeratosis.[9,72,74,75,104-110] Risk factors for development of malignancies are prolonged duration, large size, linear distribution, older age, immunocompromise and ionizing radiation. Linear porokeratosis is the commonest variant to become malignant (20%). Other variants which have been reported to undergo malignant transformation are porokeratosis of Mibelli (7.5%), porokeratosis palmaris et plantaris and disseminated superficial actinic porokeratosis (3.4%). Porokeratosis ptychotropica has been reported to turn malignant in a single patient. The pathomechanism behind malignant transformation is not clear, but chromosomal instability and reduced immunesurveillance with overexpression of p53 are thought to contribute.[111-113] Rarely, squamous cell carcinoma developing in porokeratosis may metastasize, leading to death of the patient.[114]

A few cases of melanoma have also been reported in porokeratosis.[115] Melanocytic hyperplasia in porokeratotic lesions, especially disseminated superficial actinic porokeratosis, has been demonstrated probably due to high UV exposure leading to this condition.

Treatment

General measures include avoidance of triggering factors and addressing the underlying cause of immunosuppression (if any). Strict photo protection and application of sunscreens and emollients are advisable. Looking out for any signs of malignancy is another corner stones of management.

Topical measures

- Steroids: Because of their anti-inflammatory properties, they provide relief in cases associated with itching and burning.
- 5-fluorouracil: It interferes with DNA replication and transcription of DNA to RNA and acts by down regulating the proliferation of abnormal keratinocytes.

1–5 % 5-fluorouracil cream may be used thrice weekly, till ulceration develops.[116]

- Vitamin D analogs: They down regulate the calcium induced differentiation of keratinocytes. Twice-daily application of calcipotriene cream (0.005%) or tacalcitol gives good results, especially in disseminated superficial actinic porokeratosis.[117,118]
- Retinoids: They reduce the proliferation of abnormal keratinocytes, thereby decreasing the chance of malignant transformation as well. Tretinoin 0.025% and 0.05% creams can be used.
- Imiquimod 5% cream: It acts through Toll-like receptors and induces the secretion of interferon-alpha, leading to regression of the lesions of porokeratosis.
- Topical diclofenac (3%) cream: This has been shown to provide good results

Systemic measures

- Retinoids: Oral isotretinoin 0.25 – 1.5mg/kg/d has been shown to provide satisfactory results.[119] It may be combined with topical 5-fluorouracil[120] Etretinate has also been used successfully in cases of disseminated porokeratosis.[121]Acitretin is another good option. Retinoids are continued till complete resolution of lesions. They should be avoided in women of reproductive age due to possibility of teratogenicity.

Procedures

Surgical excision,[122] diamond fraise dermabrasion, CO2 laser,[123] pulsed dye laser,[124] erbium laser[125] or cryotherapy are indicated when medical therapy does not give satisfactory results. Laser therapy may bring satisfactory cosmetic results when it comes to disseminated superficial actinic porokeratosis, porokeratosis of Mibelli and reticulate porokeratosis. Surgical treatment and cryotherapy are preferred in areas where topical agents are contraindicated or difficult to be applied. If malignant transformation is suspected, a skin biopsy or surgical excision with histopathology is mandatory.

Newer modalities

- Photodynamic therapy has been recently tried, with some beneficial effects reported.[126]
- Treatment with inhibitors of HMG-CoA reductase or other preceding steps in the mevalonate biosynthetic pathway may represent a future therapeutic approach.[127]
- Ingenol mebutate and oral alitretinoin have been tried with favorable results.[128]

Conclusion

Porokeratosis is usually a benign dermatosis, except some variants (linear and giant) where aggressive treatment is required to prevent the development of malignancies. Patients with genitocrural porokeratosis, disseminated superficial actinic porokeratosis and disseminated superficial porokeratosis are often difficult to manage and the search for an effective and safe modality goes on. The abnormalities in mevalonate metabolism now being the prime pathogenetic theory, future therapeutic modalities of this enigmatic disease may likely be based on this pathway.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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