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Review Article

Unravelling Porokeratosis: A Complex Keratinization Disorder with Malignant Potential.

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Abstract:
Porokeratosis is a group of keratinization disorders with heterogeneous clinical presentations, characterized by annular plaques with hyperkeratotic rims known as cornoid lamellae. Genetic mutations, particularly in the mevalonate pathway, underlie the disease, with environmental triggers like ultraviolet (UV) radiation and immunosuppression playing contributory roles. Several clinical forms exist, including disseminated superficial actinic porokeratosis (DSAP), linear porokeratosis, and porokeratosis of Mibelli. While typically benign, porokeratosis has a potential for malignant transformation, particularly into squamous cell carcinoma (SCC). This review delves into the pathogenesis, clinical features, diagnosis, and therapeutic options for porokeratosis, with a focus on emerging genetic findings.

Keywords: Cornoid lamella, Porokeratosis,Keratinization, Mevalonate pathway

Introduction:
Porokeratosis was first described by Mibelli in 1893, presenting as a distinct disorder with characteristic histopathological findings.[1]Clinically, it manifests as atrophic plaques with a raised keratotic ridge, which correlates with the histological finding of the cornoid lamella.[2] The disorder includes a variety of clinical subtypes, with disseminated superficial actinic porokeratosis (DSAP) being the most common.[3]
The aetiology of porokeratosis remained obscure until recent research uncovered its genetic roots, specifically implicating mutations in the mevalonate pathway, which is crucial for cholesterol biosynthesis and keratinocyte differentiation.[4]Immunosuppression, ultraviolet (UV) exposure, and genetic predispositions have been shown to play key roles in its pathogenesis. The aim of this review is to discuss the clinical, pathological, and therapeutic aspects of porokeratosis and explore the molecular mechanisms that contribute to its development.

Pathogenesis:
Mutations in the mevalonate pathway are central to the pathogenesis of porokeratosis.[5-6]Key genes involvedinclude *MVK*(mevalonate kinase), *PMVK* (phosphomevalonate kinase), and *MVD* (mevalonate diphosphate decarboxylase). These enzymes are essential for cholesterol synthesis, and their dysfunction leads to the abnormal differentiation of keratinocytes, resulting in the characteristic lesions of porokeratosis.
The two-hit hypothesis has been proposed to explain the occurrence of porokeratosis. A germline mutation in one allele of a gene involved in the mevalonate

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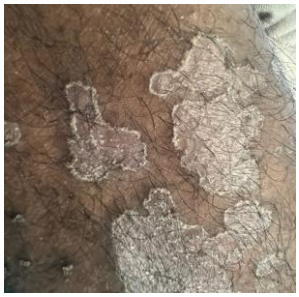
pathway, followed by a second somatic mutation triggered by environmental factors like UV radiation, results in the localized manifestation of the disease.[7-10] This model helps explain why porokeratosis tends to develop on sun-exposed areas, especially in forms like DSAP.[10] Other triggers include immunosuppression, which may exacerbate the progression of the disease.[11]

Clinical Features: Porokeratosis presents with a spectrum of clinical manifestations, depending on the variant:

1. **Porokeratosis of Mibelli**: This is the classical form, presenting as single or multiple plaques with a raised keratotic border, most commonly appearing during childhood.[12]
2. **Disseminated Superficial Actinic Porokeratosis (DSAP)**: DSAP is the most common variant and presents as multiple small, hyperkeratotic papules on sun-exposed areas such as the forearms and legs.[13] It typically appears in adulthood and is more frequent in women.[14]
3. **Linear Porokeratosis**: This form follows the lines of Blaschko, appearing in childhood, and has a higher risk of malignant transformation to SCC.[15]
4. **Punctate Porokeratosis**: This variant presents with small, seed-like papules on the palms and soles, making it difficult to diagnose.[16]
5. **Porokeratosis Ptychotropica**: Characterized by pruritic, red-to-brown plaques in the intergluteal cleft and buttocks, this rare variant presents as coalescent papules that may progress to SCC.[17]
6. **Disseminated Superficial Porokeratosis (DSP):** Lesions are widely distributed, resembling DSAP, but they are not limited to sun-exposed areas.



Picture 1: Disseminated Superficial Porokeratosis seen as multiple plaques with raised keratotic rim.

7.**Solar Facial Porokeratosis:** Thin papules appear on the face, primarily affecting young women, especially of Asian descent, and may be pigmented.

8. **Porokeratosis Palmaris et Plantaris et Disseminata (PPPD):** Involves papules on the palms and soles, along with the trunk, limbs, and even mucous membranes; it typically begins in childhood or adolescence.

9. **Localized Genital Porokeratosis:**Most commonly found on the scrotum, followed by the penis; genital involvement may also occur in other forms of porokeratosis.

10.**Eruptive Disseminated Porokeratosis:** Sudden onset of numerous, widespread, inflamed keratoses, which may be itchy and can resolve on their own; in about 30% of cases, it may be associated with an underlying malignancy.

11.**Porokeratoma:** Typically affects the extremities but can also occur on the buttocks or within the intergluteal cleft.

The common histological hallmark across all variants is the presence of the cornoid lamella, a column of parakeratotic cells overlying a thinned granular layer.[18]

Malignant Potential:
Porokeratosis carries a risk of malignant transformation, most notably to SCC, but also to basal cell carcinoma (BCC) and, in rare cases, melanoma.[19]The risk is particularly elevated in longstanding lesions, such as those seen in linear porokeratosis and immunosuppressed individuals.[20] Studies have shown that up to 7-11% of patients with porokeratosis may develop SCC or BCC over time.[21] Therefore, regular dermatological surveillance is essential for early detection of malignancies.

Diagnosis:
Diagnosis of porokeratosis is based on clinical presentation and histopathology.[22] The presence of a cornoid lamella is diagnostic, and it can be visualized using dermoscopy or histological examination.[23]Dermoscopy often reveals a thin, keratotic ridge corresponding to the cornoid lamella.[24] Reflectance confocal microscopy is another tool that aids in visualizing this diagnostic feature.[25]In familial cases, genetic testing can help confirm mutations in the mevalonate pathway genes.[26]

Treatment:
There are limited effective treatments for porokeratosis, and management primarily involves symptomatic relief and prevention of malignant transformation. Topical agents like 5-fluorouracil, retinoids, and calcipotriol are commonly used.[27] Photodynamic therapy (PDT) has shown efficacy, especially in DSAP.[28] Cryotherapy, laser therapy, and surgical excision are options for localized lesions,

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particularly those with a risk of malignant transformation.[29] Emerging therapies targeting the mevalonate pathway, such as statins and cholesterol-lowering agents, are being investigated as pathogenesis-directed treatments.[30]

Regular follow-up is critical for monitoring the progression of lesions and for early detection of malignancies, particularly in patients with high-risk forms such as linear porokeratosis.[31]

Conclusion:

Porokeratosis is a complex keratinization disorder with a significant risk for malignant transformation, particularly to SCC. Advances in understanding the genetic basis of porokeratosis, especially the role of the mevalonate pathway, have opened new avenues for targeted therapies. However, current treatments remain limited, and ongoing monitoring for cancer development is essential. Further research is needed to explore more effective therapies, particularly those targeting the underlying molecular mechanisms of the disease.

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