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Review Article

Erythrokeratodermia variabilis et progressiva: clinical features, molecular insights, and therapeutic perspectives

Nayeli Tatiana Medina España[1]*, Martha Castro Carranza[1], Claudia Baños Segura[2]

[1]Valentín Gómez Farías General Hospital, Guadalajara, Jalisco, México
[3]Dr. Eduardo Liceaga General Hospital of Mexico city, Mexico

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***Correspondence:**
Dr. Nayeli Tatiana Medina España,
E-mail: nayeli.medina@alumnos.udg.mx

ABSTRACT

Erythrokeratodermia variabilis et progressiva (EKVP) is a rare genodermatosis characterized by transient, erythematous patches and persistent hyperkeratotic plaques with a highly variable clinical presentation. As a disorder predominantly linked to pathogenic variants in GJB3 and GJB4, encoding connexin proteins essential for intercellular communication, EKVP highlights the critical role of gap junction integrity in epidermal homeostasis. This article aims to provide a comprehensive overview of EKVP, focusing on its clinical manifestations, pathophysiological mechanisms, and the role of molecular diagnostics in confirming the diagnosis. Additionally, emerging treatment strategies, including targeted therapies and advances in genetic counseling, are discussed. Enhanced understanding of EKVP's molecular underpinnings has paved the way for innovative therapeutic approaches, offering new hope for affected individuals.

Keywords: Erythrokeratodermia variabilis et progressiva, Genodermatosis, Connexins, GJB3, GJB4, Skin diseases, Hyperkeratosis, Genetic mutations, Targeted therapies

INTRODUCTION

Erythrokeratodermia variabilis et progressiva (EKVP) is a genetically heterogeneous group of rare cutaneous disorders first described in the early 20th century. This condition is part of the erythrokeratodermas, characterized by dynamic, sharply demarcated erythematous lesions and variable degrees of hyperkeratosis. Clinically, EKVP is marked by its dual phenotypic presentation: transient erythematous patches that fluctuate in response to environmental and emotional triggers and persistent hyperkeratotic plaques often distributed symmetrically on extensor surfaces.[1,2]

EKVP is predominantly caused by mutations in genes encoding connexins, particularly GJB3 and GJB4. These genes encode connexin 31 and connexin 30.3, respectively, integral proteins in gap junctions that facilitate cellular communication and homeostasis. Disruption in gap junction functionality leads to altered keratinocyte differentiation and proliferation, manifesting as the hallmark skin changes seen in EKVP. While the condition is typically inherited in an autosomal dominant manner, sporadic cases have been documented, further expanding the spectrum of its genetic and phenotypic variability.[1,2]

Despite its rarity, EKVP has significant implications for affected individuals due to its chronic course, cosmetic impact, and associated psychosocial burden. Traditional treatment approaches have centered on symptomatic relief, with variable efficacy. However, advances in understanding the molecular mechanisms underlying EKVP have prompted the exploration of novel, targeted therapies.[3]

This review aims to provide a detailed examination of EKVP, integrating clinical observations with molecular insights to underscore the importance of precise diagnosis and innovative management strategies. By delving into the pathophysiological intricacies and therapeutic developments, we seek to illuminate pathways for

improved patient care and future research directions in this rare dermatological disorder.[3]

EPIDEMIOLOGY

EKVP is an exceedingly rare genodermatosis, with an incidence that remains largely undetermined due to its rarity and underreporting in the medical literature. Its prevalence is believed to be higher in populations with established consanguinity, although the condition is typically inherited in an autosomal dominant fashion. Sporadic cases, however, have been documented, which may arise due to de novo mutations or autosomal recessive inheritance patterns in specific familial clusters.[4]

EKVP affects individuals across all ethnic and racial groups, with no significant predilection noted for either sex. Cases have been reported worldwide, although most of the published literature originates from case studies or series in Europe, North America, and Asia. This geographic distribution may reflect differences in healthcare access, diagnostic capabilities, and reporting practices rather than true epidemiological variations.[4]

The onset of EKVP typically occurs in infancy or early childhood, with most cases presenting within the first year of life. However, late-onset presentations have also been described, highlighting the clinical heterogeneity of this condition. Early recognition is crucial for diagnosis, as the transient nature of the erythematous patches and the variability in hyperkeratotic manifestations can lead to diagnostic delays. Furthermore, mild or atypical cases may remain undiagnosed, contributing to the condition's apparent rarity.[4]

From a genetic perspective, the disorder is most commonly associated with mutations in the GJB3 and GJB4 genes, which encode connexin 31 and connexin 30.3, respectively. These connexin mutations are critical to the disease's pathogenesis and show variable penetrance, further complicating the epidemiological characterization of EKVP. Other connexin-related disorders may occasionally mimic EKVP, leading to diagnostic overlap and challenges in distinguishing this condition from other erythrokeratodermas or genodermatoses with similar phenotypes.[4]

The familial clustering of EKVP emphasizes its genetic basis. Pedigree analyses reveal autosomal dominant inheritance patterns in most cases, with high penetrance but variable expressivity. This variability likely accounts for the significant phenotypic differences observed within affected families, ranging from mild erythematous lesions to extensive hyperkeratotic plaques.[5]

While EKVP itself is not associated with systemic involvement, its chronic and often disfiguring nature imposes a significant psychosocial burden on affected individuals. The visible skin lesions may lead to stigmatization, reduced quality of life, and psychological distress, particularly in societies where physical appearance heavily influences social interactions. These factors underline the importance of raising awareness about the condition among healthcare providers and the general population to facilitate earlier diagnosis and management.[5]

In summary, EKVP is a rare, genetically driven dermatological disorder with a global distribution. Its precise epidemiology remains challenging to ascertain due to underreporting, diagnostic variability, and phenotypic heterogeneity. Ongoing advancements in genetic research and increased recognition of the disorder may help to elucidate its true prevalence and improve outcomes for affected individuals.[5]

CLINICAL MANIFESTATIONS

EKVP is characterized by a wide spectrum of clinical manifestations that vary in both intensity and presentation, making it a diagnostic challenge in dermatology. The hallmark features of EKVP are the intermittent erythematous patches and the persistent hyperkeratotic plaques, which collectively contribute to its unique and often variable clinical profile. The disease is classically distinguished by its episodic and progressive nature, with fluctuating lesions that often change in response to external stimuli.[6]

Erythematous patches

The most prominent clinical feature of EKVP is the presence of well-demarcated, erythematous patches that appear acutely and fade within days to weeks. These patches are typically symmetrically distributed on the extensor surfaces, including the limbs, trunk, and face. They are characteristically triggered or exacerbated by environmental factors such as temperature changes, humidity, and emotional stress. The erythematous lesions may vary in size and shape, and they often exhibit a transient, migratory pattern, with new patches appearing while others resolve. The degree of erythema can range from mild to intense, and in some cases, these patches may present with accompanying mild scaling.[6]

Hyperkeratotic plaques

In addition to the transient erythematous patches, EKVP is also characterized by the presence of persistent hyperkeratotic plaques that develop over time. These plaques typically appear as thickened, dry, and scaly areas of the skin. They are often most pronounced on the extensor surfaces such as the elbows, knees, and shins, but can also be found on the palms, soles, and scalp. The plaques may be localized or widespread, and they can become more pronounced with age, particularly in individuals who have had the condition since infancy. The severity of the hyperkeratosis can vary, with some individuals experiencing only mild scaling, while others

may develop thick, verrucous plaques that can become fissured and prone to secondary infection.[7]

Pachyonychia

Pachyonychia, or thickening of the nails, is another common manifestation seen in individuals with EKVP. Nail abnormalities may include subungual hyperkeratosis, thickening of the nail plate, and irregular nail growth. The nails may become brittle and discolored, and in some cases, there may be painful nail separation. These nail changes often worsen as the patient ages and may contribute to additional cosmetic and functional challenges. While not universally present, pachyonychia is a significant clinical finding when observed and can serve as an important diagnostic clue.[7]

Palmoplantar keratoderma

Palmoplantar keratoderma (PPK) is frequently observed in individuals with EKVP, manifesting as thickened, hyperkeratotic skin on the palms and soles. The appearance of the PPK can vary from fine scaling to extensive, callus-like plaques. This manifestation often leads to functional limitations due to the discomfort and the skin's reduced ability to withstand friction and pressure. In some cases, the thickening of the skin on the palms and soles can cause significant pain, cracking, and fissuring, making it challenging for affected individuals to perform activities of daily living.[7]

Confluent lesions and pigmentary changes

As the disease progresses, individuals with EKVP may develop areas where the erythematous patches and hyperkeratotic plaques merge, resulting in confluent lesions. These larger, coalesced lesions often present with a more pronounced erythema and a thickened, leathery appearance. Over time, as the skin heals and remodels, these lesions may be associated with pigmentation changes, including hyperpigmentation or hypopigmentation, particularly in areas where the skin has undergone chronic irritation or healing. These pigmentary changes, while not always present, can further contribute to the cosmetic burden of the disease.[8]

Episodic flare-ups

EKVP is a dynamic disorder with episodes of exacerbation that are often provoked by various factors such as temperature fluctuations, emotional stress, infections, or other environmental changes. These flare-ups may be characterized by a sudden onset of erythematous patches or the appearance of new hyperkeratotic lesions. The periodic nature of the flare-ups means that the clinical severity of the disease may fluctuate over time, with periods of relative calm followed by more intense outbreaks. It is common for affected individuals to experience a waxing and waning course, where symptoms are controlled or less prominent during certain periods and become more pronounced during others.[8]

Mucosal involvement

Although rare, mucosal involvement may occur in EKVP, typically manifesting as mild changes in the oral mucosa. These changes may include erythema or mild scaling of the mucosal surfaces, but they do not typically present with the same degree of severity seen in the skin. Mucosal involvement may be a less frequent manifestation, but its presence could suggest a more widespread disease process.[9]

Psychosocial impact

While not a direct dermatologic manifestation, the psychosocial impact of EKVP should not be overlooked. Due to the visible and chronic nature of the skin lesions, individuals with EKVP often experience social stigmatization, anxiety, and depression. The cosmetic concerns associated with the condition can significantly affect the patient's quality of life, particularly in cases where the lesions are extensive or resistant to treatment. Children, in particular, may be susceptible to bullying or social isolation due to the appearance of their skin, leading to significant emotional distress. Therefore, the management of EKVP must take into consideration the psychological well-being of the patient, and support from mental health professionals may be necessary for some individuals.[9]

The clinical manifestations of EKVP are diverse and complex, encompassing both erythematous patches and persistent hyperkeratotic plaques. The disease's episodic and progressive nature presents significant challenges in diagnosis and management. Understanding the full spectrum of clinical features, including secondary manifestations like nail and mucosal changes, is essential for accurate diagnosis and appropriate treatment planning. Moreover, the psychosocial effects of the condition highlight the need for a multidisciplinary approach to patient care, addressing both the physical and emotional aspects of the disease. Early recognition and comprehensive management strategies are critical in improving the quality of life for individuals living with EKVP.[10]

DIAGNOSTIC METHODS

The diagnosis of EKVP is primarily clinical, based on its characteristic presentation of transient erythematous patches and persistent hyperkeratotic plaques. However, given the significant phenotypic overlap with other hereditary and acquired keratinization disorders, a comprehensive diagnostic approach is often necessary. This includes a detailed clinical examination, thorough patient history, histopathological analysis, advanced imaging, and genetic testing. Such an approach not only confirms the diagnosis but also differentiates EKVP from

other conditions with similar manifestations, facilitating precise management.[11]

Clinical diagnosis

The cornerstone of EKVP diagnosis lies in the clinical evaluation of its hallmark features.

Erythematous patches: A detailed examination of transient, well-demarcated erythematous patches is crucial. These patches, often migratory, are examined for their location, symmetry, and triggers such as environmental changes or stress.[11]

Hyperkeratotic plaques: Persistent, thickened, scaly plaques are evaluated for their distribution (frequently on extensor surfaces), severity, and progression over time.[11]

Temporal and environmental correlations: A careful history of lesion exacerbations triggered by temperature changes, humidity, or emotional stress can provide important diagnostic clues.[11]

Family and genetic history

EKVP is primarily inherited in an autosomal dominant fashion, with mutations most commonly identified in the *GJB3*and *GJB4* genes encoding connexin 31 and connexin 30.3, respectively. A family history of similar dermatologic findings strongly supports the diagnosis. However, de novo mutations and sporadic cases necessitate further investigation to confirm the genetic etiology.[12]

Pedigree analysis: Constructing a three-generation pedigree can reveal inheritance patterns and identify other potentially affected family members.[12]

Consanguinity and ethnic background: In cases with autosomal recessive inheritance patterns, consanguinity may be explored to assess genetic predisposition.[12]

HISTOPATHOLOGY

Histopathological examination of a skin biopsy provides valuable insights into the structural changes associated with EKVP, although findings are not pathognomonic.

Key histological features include:

Orthokeratosis and parakeratosis: Alternating patterns in the stratum corneum, often reflecting the variability of the condition.[12]

Epidermal hyperplasia: Irregular acanthosis with focal hyperkeratosis.[12]

Dilated capillaries: Prominent capillary dilation in the dermis, corresponding to erythematous patches.[12]

Mild perivascular inflammation: A lymphohistiocytic infiltrate, indicative of low-grade inflammation.[12] While histopathology may suggest EKVP, the findings are not definitive and should be interpreted alongside clinical and genetic data.[12]

Genetic testing

Molecular genetic testing is the gold standard for confirming a diagnosis of EKVP, especially in atypical presentations or cases with no clear family history.[13]

Targeted gene sequencing: Analysis of GJB3 and GJB4 genes to identify pathogenic mutations.[12]

Next-generation sequencing (NGS): Comprehensive NGS panels are employed when initial gene testing is inconclusive or when differential diagnoses include other genodermatoses.[14]

Whole exome or genome sequencing: For patients with atypical phenotypes or negative targeted testing, broader genetic analyses can identify novel mutations or alternative genetic causes.[14] Genetic counseling should accompany testing to address inheritance patterns, recurrence risks, and implications for family members.[14]

Imaging and advanced diagnostic techniques

Although not routinely employed, imaging and advanced diagnostic techniques can provide supplemental information:

Dermoscopy: Non-invasive dermoscopic examination may reveal vascular patterns corresponding to erythematous patches and surface scaling associated with hyperkeratotic plaques.[14]

Reflectance confocal microscopy (RCM): High-resolution imaging of the epidermis and dermis may identify structural alterations such as keratinocyte abnormalities and vascular dilation.[14]

Differential diagnosis

Given the overlap in clinical features between EKVP and other conditions, a structured approach to exclude other disorders is essential. Key differentials include:

Other erythrokeratodermas: Syndromes such as Progressive Symmetric Erythrokeratoderma (PSEK) and keratitis-ichthyosis-deafness (KID) syndrome may mimic EKVP. Genetic testing is critical for differentiation.[14]

Ichthyoses: Disorders like ichthyosis vulgaris and lamellar ichthyosis share hyperkeratotic features but lack the migratory erythematous patches of EKVP.

Psoriasis: Chronic plaques of psoriasis can be clinically similar, but psoriatic plaques are typically associated with

nail pitting and systemic findings, distinguishable by histopathology.[14]

Atopic dermatitis: Erythematous, scaly lesions in atopic dermatitis are pruritic and linked to atopy, unlike EKVP.[14]

Functional and quality of life assessments

While not diagnostic per se, evaluating the impact of EKVP on a patient's quality of life is essential:

Dermatology life quality index (DLQI): A validated tool to assess the psychosocial burden of skin disorders.[14]

Symptom diaries: Patients may document triggers, lesion progression, and symptom severity to aid diagnostic accuracy and tailor management strategies.[14]

Laboratory tests

Routine laboratory tests are not specific for EKVP but may help rule out other conditions:

Complete blood count (CBC): To exclude systemic inflammation or infection.

Serum immunoglobulin levels: To rule out atopy or immunodeficiency in atypical presentations.[14]

The diagnostic approach to EKVP is multidisciplinary, combining clinical expertise, histopathology, and advanced molecular genetic techniques to establish a definitive diagnosis. Early recognition and differentiation from other disorders are crucial for appropriate management and genetic counseling. The integration of clinical, histological, and genetic findings provides a robust framework for diagnosing EKVP, particularly in patients with variable or atypical presentations.[14]

CURRENT TREATMENT APPROACHES FOR EKVP

EKVP remains a challenging condition to manage due to its heterogeneity in clinical presentation, variable disease progression, and limited evidence-based therapeutic options. Current treatment strategies focus on symptom control, improving quality of life, and mitigating disease exacerbations. A multidisciplinary approach, often involving dermatologists, geneticists, and mental health professionals, is essential. This section outlines the primary therapeutic modalities employed in the management of EKVP, encompassing topical, systemic, and adjunctive therapies, alongside emerging treatments targeting the molecular mechanisms underlying the disorder.[15]

Topical therapies

Topical treatments are often the first-line option in EKVP, aiming to reduce hyperkeratosis and alleviate erythema. These are particularly suitable for patients with localized or mild disease.

Keratolytic agents

Salicylic acid: Applied as creams or ointments, salicylic acid facilitates the removal of hyperkeratotic scales, improving the appearance of plaques. Concentrations of 3-6% are commonly used, with careful monitoring to prevent irritation or systemic absorption in extensive cases.[15]

Urea-based creams: Urea enhances hydration and reduces scaling, making it a preferred choice for patients with dry or fissured skin.[15]

Retinoids

Tazarotene and adapalene: These topical retinoids normalize keratinocyte differentiation and reduce hyperkeratosis. They are typically used at night to minimize irritation.[16]

Combination therapy: Retinoids may be combined with corticosteroids to enhance efficacy while minimizing local inflammation.[16]

Topical corticosteroids

Low-to-medium potency corticosteroids can be used intermittently to control erythema and inflammation, especially during acute flares. Long-term use should be avoided to prevent skin atrophy and tachyphylaxis.[16]

Vitamin D analogues

Calcipotriol, a synthetic vitamin D analogue, is used to regulate keratinocyte proliferation and differentiation. It is particularly effective when combined with topical corticosteroids.[16]

Systemic therapies

For patients with widespread or refractory disease, systemic therapies are considered to modulate the underlying pathophysiology.16

Oral retinoids

Acitretin: The most commonly prescribed systemic retinoid for EKVP, acitretin reduces keratinocyte proliferation and enhances desquamation. Doses range from 0.5 to 1 mg/kg/day, adjusted based on clinical response and tolerance.[16]

Isotretinoin: Occasionally used as an alternative, particularly in patients intolerant to acitretin.[16]

Monitoring: Regular monitoring of liver function, lipid profiles, and skeletal health is critical during retinoid

therapy due to potential adverse effects such as hyperlipidemia, hepatotoxicity, and skeletal abnormalities.[16]

Antibiotics

Antibiotics like erythromycin or azithromycin may be prescribed for their anti-inflammatory properties, particularly in patients with secondary bacterial infections or inflammatory flares.[16]

Immunomodulatory agents

Emerging evidence supports the use of immunomodulators such as cyclosporine or methotrexate in severe, refractory cases. These agents suppress inflammation and keratinocyte hyperproliferation, although their use is off-label and requires close monitoring for the adverse effects.[16]

Emerging and targeted therapies

Advances in understanding the molecular mechanisms of EKVP, particularly connexin-related mutations, have paved the way for targeted therapies.[17]

Connexin modulators

Experimental therapies targeting connexin expression or function are under investigation, offering hope for precision medicine approaches in EKVP.[17]

Gene therapy

Gene-editing techniques such as CRISPR/Cas9 hold promise for correcting pathogenic mutations in GJB3 or GJB4, though these approaches remain in the preclinical stage.[17]

Biologics

The role of biologics targeting inflammatory pathways, such as interleukin-17 (IL-17) or interleukin-23 (IL-23) inhibitors, is being explored, especially in cases with overlapping features of inflammatory dermatoses.[17]

Adjunctive and supportive therapies

Phototherapy

Narrowband UVB (NB-UVB) phototherapy has shown benefit in reducing hyperkeratosis and erythema, likely through its immunomodulatory effects. Treatment protocols typically involve 2-3 sessions per week, with gradual dose escalation.[17]

Potential risks: Chronic phototherapy can increase the risk of skin cancer and premature aging, necessitating cautious use in long-term management.[17]

Moisturizers and emollients

Daily application of moisturizers is critical to maintaining skin barrier integrity and reducing pruritus. Emollients containing ceramides or hyaluronic acid are particularly beneficial.[17]

Psychological support

Given the significant psychosocial impact of EKVP, addressing mental health through counseling or support groups is vital.[17]

Lifestyle modifications and preventive measures

Trigger avoidance

Identifying and minimizing exposure to environmental triggers such as temperature extremes, friction, or emotional stress can significantly reduce disease exacerbations.[17]

Clothing and skin care

Loose-fitting, breathable clothing and gentle skin care products are recommended to avoid irritation.[17]

Nutritional support

Adequate hydration and a balanced diet rich in omega-3 fatty acids may support overall skin health.[17]

The management of EKVP necessitates a tailored approach, balancing efficacy and safety while considering disease severity, patient preferences, and quality of life. While current therapies focus on symptom alleviation, ongoing research into the genetic and molecular basis of EKVP holds promise for the development of targeted, curative treatments in the future. Multidisciplinary collaboration and patient-centered care remain pivotal in optimizing outcomes for individuals affected by this rare and complex disorder.

CONCLUSION

EKVP is a rare genodermatosis that exemplifies the intersection of genetic complexity and clinical heterogeneity. This disorder, characterized by migratory erythematous plaques and persistent hyperkeratosis, stems from mutations in connexin-encoding genes (GJB3, GJB4, and occasionally GJA1), which disrupt the crucial intercellular communication pathways mediated by gap junctions. These molecular aberrations manifest in diverse phenotypic presentations, ranging from localized, mild disease to extensive and debilitating cutaneous involvement.

The clinical course of EKVP is highly variable, with symptoms often appearing in infancy or early childhood and persisting throughout life. While the migratory nature

of erythematous lesions remains a hallmark, the progression to fixed hyperkeratotic plaques contributes significantly to the chronicity and psychosocial burden of the condition. The unpredictable disease trajectory and its impact on physical appearance underscore the necessity for personalized management strategies.

Diagnosis relies on a combination of clinical evaluation, histopathological findings, and genetic testing, emphasizing the importance of a multidisciplinary approach. Advances in genomic technologies have enhanced diagnostic accuracy and facilitated the identification of pathogenic mutations, providing valuable insights into disease mechanisms. However, a definitive genotype-phenotype correlation remains elusive, complicating prognostication and therapeutic decision-making.

Treatment of EKVP is primarily symptomatic, with an emphasis on mitigating hyperkeratosis, controlling erythema, and improving quality of life. Topical agents, including keratolytics, retinoids, and corticosteroids, form the cornerstone of therapy for localized disease, while systemic retinoids are reserved for severe or refractory cases. Adjunctive modalities, such as phototherapy and supportive skin care, play a critical role in comprehensive disease management. Emerging therapies targeting the molecular underpinnings of connexin dysfunction hold promise for more effective and targeted interventions in the future.

Despite these advancements, EKVP remains an area of unmet clinical need. The rarity of the condition, coupled with its phenotypic variability, poses challenges to conducting large-scale clinical trials and developing evidence-based guidelines. Furthermore, the psychosocial ramifications of living with a visible and chronic skin disorder necessitate holistic care that addresses both physical and emotional well-being.

In conclusion, while significant progress has been made in understanding the genetic and molecular basis of EKVP, ongoing research is imperative to elucidate its pathophysiology further and develop innovative therapies. A multidisciplinary approach, integrating dermatological expertise, genetic counseling, and psychological support, is essential to optimize patient outcomes. The evolving landscape of precision medicine offers hope for targeted and potentially curative treatments, paving the way for a future where the burden of EKVP can be significantly alleviated.

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