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Case Report

Clinical diagnosis of Kindler Syndrome: A report of two cases from a district hospital in Gujranwala, Pakistan

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Abstract Kindler syndrome is a rare autosomal recessive disorder belonging to the group of Epidermolysis Bullosa (EB), which encompasses genetic disorders affecting the skin and mucous membranes. This case report aims to contribute to the limited literature on Kindler syndrome by presenting two cases observed at a district hospital in Gujranwala, Pakistan. The cases involve a brother and sister displaying typical symptoms and having a family history of the disease. The objective is to enhance clinicians' awareness of this rare disorder and emphasize the significance of clinical diagnosis-driven management strategies.

Key words
Kindler syndrome; Epidermolysis Bullosa; Blisters; Photosensitivity disorders; Recessive genes.

Introduction

Kindler syndrome is a rare autosomal recessive genodermatosis reported by Theresa Kindler in 1954.[1] It is caused by a deficiency in the "kindlin 1" protein.[2] Kindler syndrome was once classified as a poikilodermatous disorder, which includes hyperpigmentation, hypopigmentation, and telangiectasia. However, telangiectasia is not a characteristic feature of Kindler syndrome. In 2008, it was reclassified as a subtype of Epidermolysis bullosa due to its shared clinical features of blister formation and genetic characteristics.[3]

The underlying etiology of Kindler syndrome can be attributed to mutations in the FERMT1 gene, responsible for encoding the protein kindlin-1. This protein plays a crucial role in facilitating the attachment of intracellular actin cytoskeleton to the extracellular matrix in epithelial tissues.[4,5] The absence of kindlin-1 within epidermal keratinocytes leads to the inactivation of integrin proteins, resulting in abnormal cellular adhesion, proliferation, chemotaxis, and subsequent fibrosis.[3,6]

Clinically, Kindler syndrome presents with trauma-induced blistering in infancy, followed by photosensitivity, poikiloderma, and cutaneous atrophy.[3,7] Progressive changes can lead to webbing of the hands and feet, abnormal pigmentation, nail abnormalities, and urological and alimentary canal symptoms.[8,9] Patients with Kindler syndrome have an increased risk of developing bladder transitional cell carcinoma and squamous cell carcinoma of the skin.[3,4,7,8]

In 2004, Fischer *et al*. presented clinical diagnostic criteria for Kindler syndrome for accurate identification of the condition **(Table 1)**. This report presents two cases of Kindler syndrome from the Gujranwala region in Pakistan, highlighting the clinical features of the

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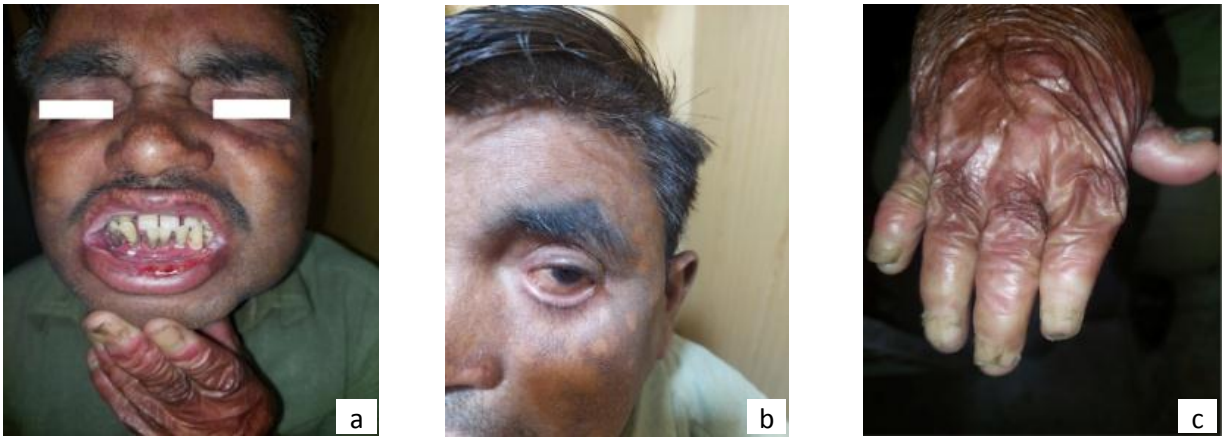

Figure 1 Manifestations of Kindler Syndrome. a) Erosions on his lips, gingivitis, periodontitis, and dental caries. b) Corneal scarring, ectropion, and arcus senilis. c) Long cuticles, subungual hyperkeratosis, and a central longitudinal ridge in the middle finger nail.

Table 1 Diagnostic criteria for Kindler Syndrome.

Major criteria
Acral blistering in infancy and childhood
Progressive poikiloderma
Skin atrophy
Abnormal photosensitivity
Gingival fragility and/ or swelling
Minor criteria
Syndactyly
Mucosal involvement (urethral, anal, esophageal, laryngeal stenosis)
Associated findings
Nail dystrophy
Ectropion of lower lid
Palmoplantar keratoderma
Pseudoainhum
Leucokeratosis of the lips
Squamous cell carcinoma
Anhidrosis/ hypohidrosis
Skeletal abnormalities
Poor dentition/ dental caries
Periodontitis[10]

disease. By expanding our understanding of Kindler syndrome and its manifestations, this study aims to contribute to improved diagnosis and management strategies.

Case reports

Case 1: A 35-year-old Pakistani male of Asian ethnicity, presented with symptoms of photosensitivity and blistering lesions on his acral areas since birth. He had a family history of Kindler Syndrome in his paternal cousin, but his parents and elder brother did not have any skin issues. Throughout his life, he experienced blistering lesions following mechanical insult, although it decreased with age. He also had erosions on his lip and inside the oral cavity, along with gingivitis, periodontitis, dental caries, and difficulty in swallowing solid foods due to esophageal strictures **(Figure 1a)**. Ophthalmologic examination revealed corneal scarring, ectropion, and arcus senilis **(Figure 1b)**. Cutaneous examination of his upper limb showed atrophic scarring with a shiny cigarette paper-like appearance, multiple hyperpigmented and hypopigmented patches on the forearms, and loss of palmar creases. Noteworthy findings on the nails included long cuticles extending up to 1/4 of the nail, subungual hyperkeratosis in both thumbs, and a central longitudinal ridge in the middle finger **(Figure 1c)**. On the dorsal surface of his feet, atrophic skin with hyperpigmentation and hypopigmentation, as well as crusting on the soles, were observed.

Case 2: A 40-year-old unmarried woman, sought medical attention at the dermatology outpatient clinic of DHQ, Gujranwala. She presented with pruritus and vesiculobullous lesions on the acral areas since birth which was exacerbated by sun exposure and scarring. Her

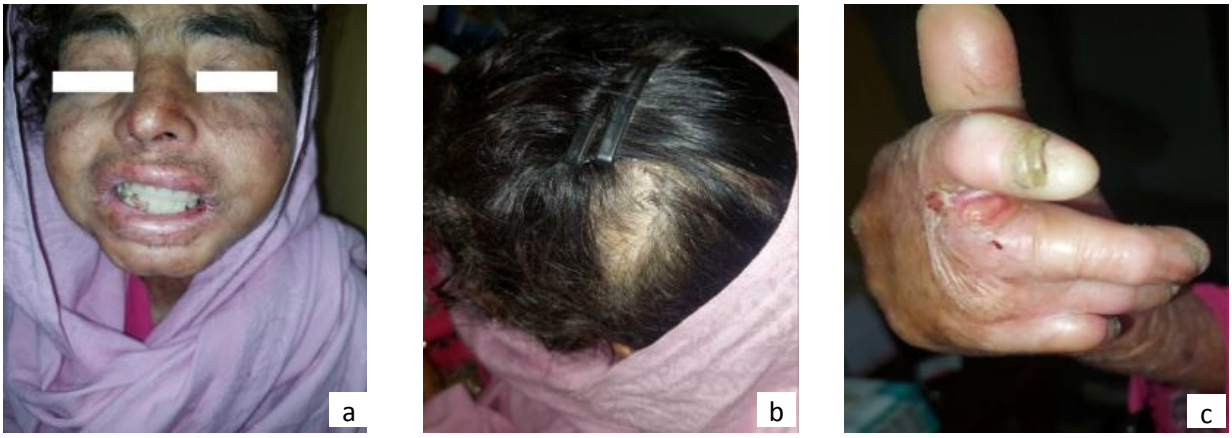

Figure 2 Manifestations of Kindler Syndrome. a) Poikiloderma on the lips along with angular cheilitis. b) Diffuse hair loss over the scalp. c) Interdigital erosion, onycholysis, subungual hyperkeratosis in the nail bed, crumbled nail matrix, pseudoainhum, and contracture.

skin was photosensitive and prone to blistering upon abrasion, and she exhibited poikiloderma on the lips along with angular cheilitis **(Figure 2a)**. Diffuse hair loss over the scalp was evident **(Figure 2b)**, as well as subungual hyperkeratosis. She reported difficulty swallowing solid foods due to esophageal strictures, necessitating the crushing of oral medications. Similar to patient "A" she experienced temporary blurred vision, burning eye pain, and excessive tearing but did not exhibit corneal erosions or erythema. Interdigital erosion **(Figure 2c)**, onycholysis, subungual hyperkeratosis in the nail bed, crumbled nail matrix, pseudoainhum, and contractures were present in both her hands and feet. Her Dermatology Life Quality Index (DLQI) score was 14, and she demonstrated an understanding of the genetic nature of her disease, although consent for oral and perianal examination could not be obtained.

Management

Comprehensive examinations were conducted, including dermal, abdominal, neurological, and cardiorespiratory assessments. The laboratory investigations did not reveal any significant findings. Based on clinical observations and in accordance with the diagnostic criteria proposed by Fischer IA *et al*., a definitive diagnosis of Kindler Syndrome was established for both patients, as they exhibited all the major criteria. Unfortunately, due to financial limitations, advanced diagnostic techniques such as immunofluorescence, genetic mapping, and electron microscopy could not be pursued.

Our management approach for Kindler Syndrome involved a multidisciplinary team to address the cutaneous manifestations. The primary goals were to alleviate symptoms, prevent complications, and improve the patients' quality of life. Treatment interventions included implementing sun protection measures, with broad-spectrum sunscreens for exposed areas, and thorough cleansing and the use of sterile or non-adherent dressings for blisters and erosions. Topical antibiotics, like Fusidic acid, were applied to prevent secondary infections and topical corticosteroids, emollients (e.g., petroleum jelly) and oral antihistamines (e.g., cetirizine or loratadine) for symptomatic relief. Collaboration with dental specialists, such as dentists or periodontists, was sought for specialized care to minimize complications such as periodontitis and dental caries. We encouraged patients to maintain a well-balanced diet and provided additional supplementation of vitamin C and zinc to support wound healing.

Over a span of two weeks, a decrease in blistering resulting from trauma was observed, attributed to careful lifestyle practices. Additionally skin hydration, wound healing, and periodontitis improved. However, symptoms such as poikiloderma, cutaneous scarring, and visual impairments persisted despite treatment measures. Both patients were advised to schedule regular follow-up visits to monitor the progression of the condition and make necessary adjustments to the treatment approach.

Discussion

This case report presents two Kindler Syndrome cases in patients "Mr. A" and "Ms. B," both with photosensitivity and blistering lesions on acral areas since birth. Patients also experienced erosions on the lip and inside the oral cavity, gingivitis, periodontitis, dental caries, and difficulty in swallowing due to esophageal strictures. Ophthalmologic examination revealed bilateral conjunctivitis, corneal scarring, ectropion, and arcus senilis. Similarities with previously reported cases included photosensitivity, blistering lesions, atrophic scarring with shiny, cigarette paper-like skin, and ocular involvement.[11] However, distinct features like skin fusion resulting in pseudosyndactyly, nail blistering leading to dystrophy, and median longitudinal fissuring with distal splitting, were also observed in our study.[12-14] We based our diagnosis of the rare disorder on clinical findings and the Fischer *et al*. diagnostic criteria.[10]

Pruritus without photosensitivity may indicate an overlapping dermatoses if environmental factors such as insect bite and mites infestation are excluded. Our patient mainly reported itching with sun exposure in photodistributed areas. They also reported an unusual exacerbation in blistering during the rainy season, which may be due to increased scratching of mosquito bites causing itchiness. Malik *et al*. has also described a case of KS where a Sarcoptesscabei infestation caused a nocturnal and generalized pattern of itching. However, the patient was diagnosed as KS on the basis of characteristic trauma induced vesicles and bullae since birth, along with photosenstivty.[15] In neonates, diagnosis is challenging as blistering resembles other forms of epidermolysis bullosa.[16] However, older children experience skin blistering, photosensitivity, and dorsal hand atrophy resembling cigarette paper, which points towards the disease.[17]

Fischer clinical diagnostic criteria (2004) for Kindler Syndrome used in our study have also been supported by Gupta *et al*. (2011) in India who identified cuticle abnormalities as a key indicator;[10,18] and Anwar *et al*. (2015) in Pakistan highlighting vesiculobullous lesions, photosensitivity, and nail degeneration.[7] Although genetic testing is crucial for accurate diagnosis and care, our study had limitations in accessing advanced diagnostic tests (immunofluorescence, genetic mapping, and electron microscopy) due to budgetary constraints. Being a case report, it lacks generalizability and causal conclusions. Long-term follow-up data is also lacking to evaluate the effectiveness of the treatment approach.

It is clear that for the treatment of Kindler Syndrome, primary focus should be on symptomatic management, requiring a multidisciplinary approach involving various specialists Dermatologists, Psychiatrists, Gastroenterologists, Dentists, Urologists, Ophthalmologists, Dieticians, and Pediatricians. Regular check-ups in dermatology clinics should be advised for surveillance of premalignant keratosis. Moreover, it sounds important for clinicians to be aware of Kindler Syndrome in patients presenting with acral vesiculobullous

diseases from birth and to consider genetic counseling upon diagnosis. A higher risk of developing cancers, such as transitional cell carcinoma of the bladder and squamous cell carcinoma of photoexposed skin, requires further research to clarify the relationship between Kindler Syndrome and malignancies. Additionally, it is crucial to explore the psychosocial effects of the condition to provide a better understanding of the disease and contribute to the development of more effective treatment strategies.

Conclusion

This study provides valuable insights into the pathogenesis and diagnosis of Kindler Syndrome. It emphasizes the importance of a comprehensive understanding of the classical features of the disease for precise diagnosis and optimal patient outcomes. By relying on clinical features, the diagnosis of Kindler Syndrome can be expedited and simplified, reducing the need for invasive and costly procedures and facilitating prompt treatment.

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