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Battling a rarity: A case of kindler syndrome from a developing country

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Abstract

Kindler syndrome, a rare branching of inherited epidermolysis bullosa, is an autosomal recessive condition characterized by the eruption of painful blisters and hemorrhagic vesicles in infancy. With age, the eruption of blisters are seen to decline leaving behind fibrosed, scarred, and paper-like skin, and poikilodermic features. To this date, about 400 cases have been reported worldwide for this disease only. This report aims to discuss the presence and diagnosis of Kindler Syndrome using limited resources in developing countries. It describes the presence of clinically diagnosed Kindler Syndrome in a young male of Pakistani descent that started in infancy and presented with a variety of clinical features over the years. Even though genetic analysis remains the gold standard diagnostic for Kindler syndrome, for third world countries, relying on Diagnostic clinical criteria remains helpful in establishing a diagnosis of Kindler syndrome for further management, as seen in our patient.

Keywords

Kindler syndrome, epidermolysis bullosa, poikiloderma, cutaneous manifestations, developing nations

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Introduction

Kindler syndrome (KS), a rare branching of inherited epidermolysis bullosa (EB), is an autosomal recessive condition characterized by the eruption of painful blisters and hemorrhagic vesicles in infancy. Eventually, with age, the eruption of blisters is seen to decline, leaving behind fibrosed, scarred, and paper-like skin and poikilodermic features. The genetic basis of this disease is seen to be associated with mutations in the *FERMT1* (*KIND1*) gene, located on the short arm of chromosome 20 (20p12.3).[1]

To this date, about 400 cases have been reported worldwide for this disease, the first-ever case being reported in 1954.[2] This case report describes the presence of clinically diagnosed KS in a young male of Pakistani descent that started in infancy and presented with a variety of clinical features over the years. This is only the second case report of KS from Pakistan.

Case presentation

A 33-year-old unmarried male of a lean built, well-oriented to time and place, presented to a tertiary care hospital with complaints of photosensitivity, discoloration, and burning of the skin upon sun exposure, dystrophic nails, watering alongside pain and redness of eyes, oral ulcers, and difficulty in passing urine. He was born out of a consanguineous marriage to parents with no history of skin disease and has four siblings who are alive and healthy. However, his family history includes a 12-year nephew with the same skin condition.

According to the patient, his symptoms started at the tender age of 5 months with the eruption of itchy, painful, and hemorrhagic blisters and vesicles, starting from his feet and soon covering the whole body. They ruptured easily, revealing blood and pus. The eruption of blisters ceased by the age of 5 years, but his skin was left pigmented with easy sunburn and redness on exposure to the sun, and distortion of his nails (Figure 1). In the recent years, he has noticed intermittent

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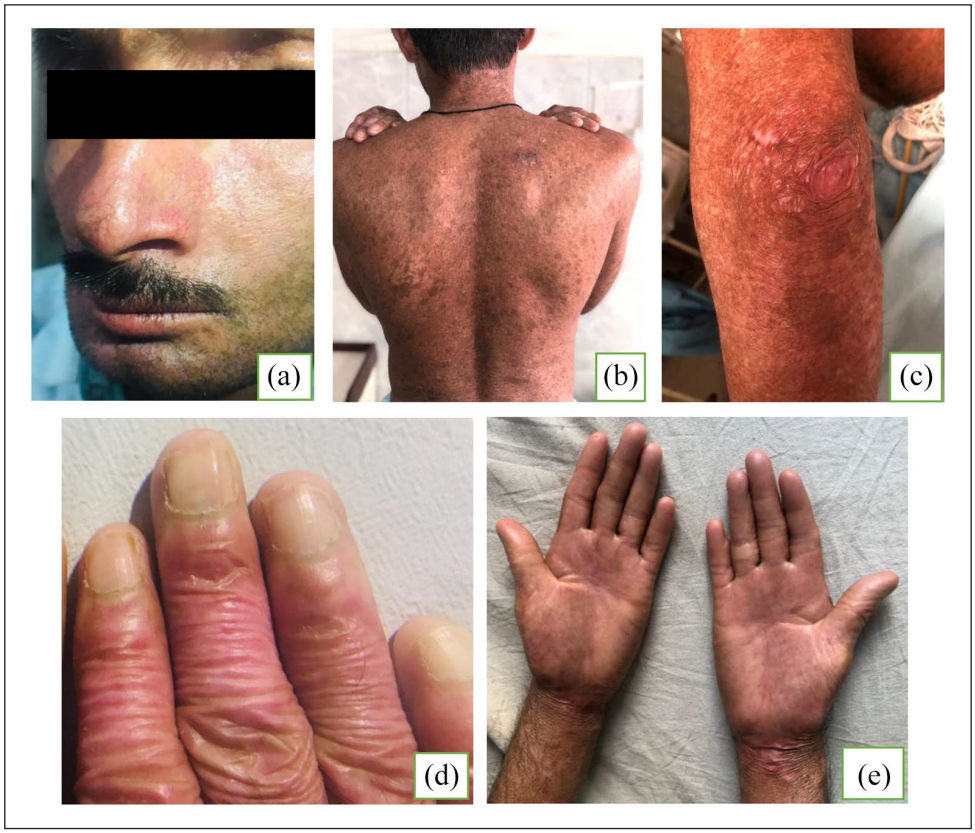

Figure 1. Cutaneous examination findings in the patient: (a) Telangectasias seen on face and arm, (b) Generalised hyper and hypopigmentation with areas of skin atrophy on neck and arms, (c) Atrophic hypo and hyperpigmented skin with areas of cigarette paper scarring especially on elbows, (d) Areas of skin atrophy on dorsal aspect of fingers and Metacarpophalangeal joints, thick, long, and ragged cuticles, roughened distorted nails, longitudinal ridges, and grooves. (e) Loss of dermatoglyphics and Keratoderma.

excessive redness and watering of the eyes alongside photosensitivity; however there is no complain of decreased or blurred vision. He recently observed the development of a vesicle on the medial canthus of his left eye that ruptured spontaneously. There is history of oral ulcers that self-resolve. Since the past year, he has complained of difficulty in micturition, with an increase in frequency, hesitancy, burning and the feeling of an incompletely emptied bladder; it was not associated with hematuria, pyuria, or frothy urine. No evidence of Raynaud's phenomenon, genital ulcers, alopecia, or arthralgia was seen. There is no history of comorbidities like hypertension, Diabetes Mellitus, Tuberculosis or any chronic infections. The rest of his systemic examination was unremarkable.

Cutaneous examination of the patient revealed generalized hypo and hyperpigmented skin with areas of skin atrophy and telangiectasias seen on the face, neck, and arms alongside palmoplantar keratoderma, loss of dermatoglyphics, loss of cuticles, and roughened distorted nails (Figure 1). Eye examination showed mild ectropion with misdirected eyelashes causing irritation (Figure 2(a)). Loss of teeth was observed with the exception of three premolar teeth (Figure 2(b)).

To reach a diagnosis, multiple investigations were carried out starting from baseline blood investigations that appeared within optimal range. X-ray chest and pelvis were unremarkable. However, ultrasound of the abdomen revealed a thick-walled bladder, indicating a bladder outflow obstruction. Urine cultures sent on two separate occasions, 1 month apart, indicated infection, first by *Pseudomonas aeruginosa* and then by *E. coli*. A urethrogram was carried out which concluded the presence of a bladder that is irregular in outline with multiple sacculations and few diverticulae with significant post-void contrast. An irregular and narrow-caliber penile and bulbar urethra with partial stricture at bulbomembranous junction was also seen. Moreover, his Anti Nuclear Antibody and anti-dsDNA antibody titres were negative.

To reach a final diagnosis, a biopsy was done from the poikilodermic skin of the back that showed focal severe acute-on-chronic necrotizing inflammation with epidermal atrophy, and presence of congested vessels and focal pigmentary incontinence in the dermis, findings all favoring KS. Unfortunately, due to lack of financial support, immunofluorescence and genetic analysis could not be carried out.

Management of the patient's condition started with the involvement of a multidisciplinary team alongside

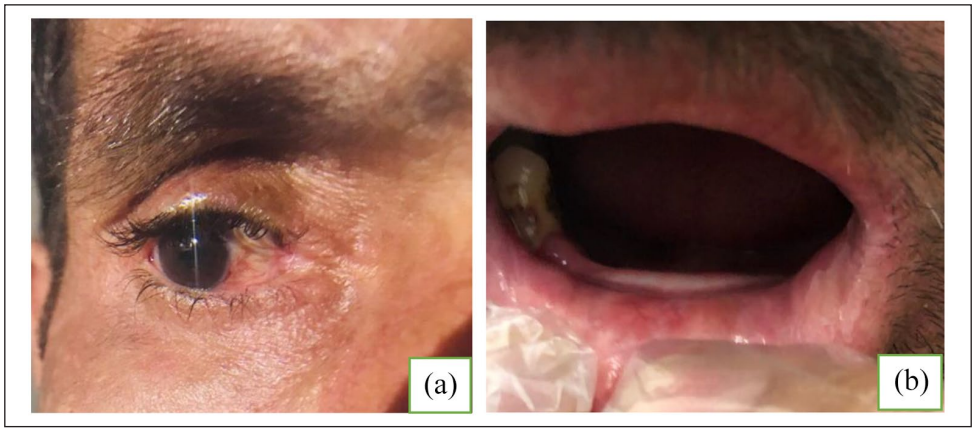

Figure 2. (a) Ocular examination revealed mild ectropion with distorted architecture of the medial canthus and conjunctivitis because of misdirected lashes. (b) Oral cavity examination revealed restricted mouth opening, angular cheilitis, and loss of all teeth except three premolar teeth.

symptomatic and preventive treatment to improve quality of life of the patient. Interventional management included suprapubic catheterization of the patient along with a plan to improve the stricture of bulbar and penile urethra with surgical intervention. Epilation was carried out to relieve trichiasis. Dental extraction and dental prosthesis were advised.

Medications prescribed included Amikacin, Omeprazole, antihistamines, and multivitamins. Multiple eye drops and the use of broad-spectrum sunblock were advised. Patient was counseled for proper hygiene of the skin, limited sun exposure, and prevention of skin trauma. Negative counseling for consanguineous marriage was carried out. Over the next few days, a general improvement in wound healing and skin hydration was seen. However, the clinical features of KS, such as poikiloderma, photosensitivity, and skin scarring remained the same. The patient was advised to regularly follow-up in the out-patient department.

Discussion

KS is a rare subtype of EB with an autosomal recessive pattern of inheritance that has usually been described in individuals mainly of Arab, Pakistani, Indian, Iranian, and Turkish origins. It has also been identified in European individuals, especially those of British Caucasian, Albanian, Italian, and Serbian origin.[3–5] It is characterized by acral blistering (trauma-induced), followed by skin atrophy (leading to cigarette-paper skin) and persistent poikiloderma alongside a degree of photosensitivity and poikiloderma on sun-exposed areas. Other features include pseudosyndactyly, ainhum (band of fibrous tissue around the base of the toe), nail dystrophy, palmoplantar keratoderma, keratoconjunctivitis, conjunctival scarring, ectropion, and anemia.[1,3,6] Involvement of mucous membranes leads to loss of teeth, esophageal strictures, phimosis, and even severe disability on account of stenosis of mucosal cavities. The histopathological features in light microscopy are nonspecific and comprise attenuated and flattened epidermis, hydropic alteration with cleft formation, and colloid bodies. The dermis is found to contain dilated vessels with dermal edema and moderate fibrosis.[7] Transmission electron microscopy shows major disorganization of the basement membrane with single or multiple cleavage planes and reduplication of the lamina densa.[1]

KS can be diagnosed by clinical findings and the detection of the *FERMT1* gene mutation. The *FERMT1* gene encodes the Kindlin-1 protein, which is a constituent of focal adhesions that help bind actin filaments in basal keratinocytes to the underlying extracellular matrix.[6,8] Angelova–Fischer and colleagues proposed a set of clinical diagnostic criteria for KS (Table 1).[9] The main diagnosis criterion remains the genetic analysis of the *FERMT1* gene mutation, and the aforementioned criteria is employed only if a genetic test is not available, as in our case. Since our patient presented with all five major features, a certain diagnosis of KS was established.

As part of the clinical strategy, several illnesses that can result in comparable symptoms must be distinguished from KS.[10,11] Rothmund-Thomson Syndrome, Xeroderma Pigmentosum, Bloom Syndrome, Cockayne Syndrome, Dyskeratosis Congenita, and EB are some of the differential diagnosis of KS.[1]

Patients with Rothmund-Thomson syndrome have cataracts, hypogonadism, and sparse hair in addition to poikiloderma and photosensitivity, which are not present in KS, as in our patient. Extreme photosensitivity, pigmentary, and poikilodermatous alterations on photoexposed skin are the hallmarks of the autosomal recessive condition Xeroderma pigmentosum, which lacks the skin fragility in the form of acral bullae as seen in KS. These patients may potentially have several neurological abnormalities in addition to early-onset skin malignancies. Without exhibiting true poikiloderma, patients with Bloom's syndrome exhibit photosensitivity, telangiectasias, and erythema of the sun-exposed areas. This condition is also characterized by short stature, frequent

Table 1. Criteria for the diagnosis of KS proposed by Angelova–Fischer and colleagues; 4 major criteria present- diagnosis is certain, 3 major and 2 minor criteria—diagnosis is probable, 2 major and 2 minor criteria are present-diagnosis is likely.

Major criteria	1. Acral blistering in infancy and childhood
	2. Progressive poikiloderma
	3. Skin atrophy
	4. Abnormal photosensitivity
	5. Gingival fragility and/or swelling
Minor criteria	1. Syndactyly
	2. Mucosal involvement: urethral, anal, esophygeal, and laryngeal stenosis
Associated findings	i. Nail dystrophy
	ii. Ectropion of the lower lid
	iii. Palmoplantar keratoderma
	iv. Pseudoainhum
	v. Leucokeratosis of the lips
	vi. Squamous cell carcinoma
	vii. Anhidrosis/hypohidrosis
	viii. Skeletal abnormalities
	ix. Poor dentition/dental caries/periodontitis

infections, and an increased frequency of hematological malignancies. Characteristic features of Cockayne's syndrome include erythema in areas that have been exposed to light, atrophy, and hyperpigmentation. The prevalence of dwarfism, cachexia, progressive pigmentary retinopathy, deafness, and bird-like features can help to distinguish it from KS. Dyskeratosis congenita is characterized by leukoplakia, reticulated hyperpigmentation, and nail dystrophy. Bullae are seldom visible, and the pigmentary alterations are not fully poikilodermatous. None of the defining characteristics of the aforementioned illnesses were present in our case.

Patients with KS have a normal life expectancy, but they are more likely to develop complications from mucocutaneous lesions and malignancies, including squamous cell carcinoma (SCC) of the lip, hard palate, and acral skin, as well as transitional cell carcinoma of the bladder, which have a severe course.[3,12] Bacterial colonization of the numerous ulcerations might cause sepsis. The patient is unable to eat because of the oral and esophageal lesions, and malnutrition is noticed. When blisters are present on the larynx or trachea, there is a substantial risk of airway blockage. It's possible to develop phimosis, urethral strictures, or even nephrotic syndrome. Additionally, 10% of patients can develop malignant skin tumors such as SCC beyond the age of 45.[6,13] Such patients should be closely monitored. Adults with persistent wounds may develop SCC, which has an aggressive course and frequent recurrences following surgical intervention.[14]

For EB, there is no particular treatment. In order to effectively manage EB, wound care and bacterial colonization avoidance are crucial. For the prevention and treatment of complications that arise over the course of the disease, a multidisciplinary approach is essential. For infected sores and ulcerations, the use of topical and systemic antibiotics is vital for lowering morbidity. The use of moisturizers is advised (to lessen xerosis and skin fissures), alongside sun and injury prevention.[15] Adolescence is the ideal time to start premalignant keratosis screening.[16] One can utilize various foam types, altered absorbent pads, lipidocolloid dressings, contact layers, hydrogel sheets, and alginates. The decision may be hard given that there are numerous wound care solutions available and because there are no specified guidelines.[15] An individualized treatment is necessary due to the clinical diversity. Pain control is another critical component. For older lesions, debridement of the lesions is required. It is possible to utilize a variety of nociceptives, including acetaminophen and even opioids.[17] Given the possibility of carcinomas, the patient needs to be encouraged to avoid any unnecessary trauma and to use sunscreen as frequently as feasible.

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Ethics

The patient had given his informed consent for inclusion before they participated in the study, along with consent for publication.

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