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Case Report

A Very Rare Case of Kindler Syndrome

Satyam A. Parmar* and Payal D. Shah

Pathology Department, P.D.U. Medical College, Rajkot (Gujarat), India

***Correspondence Info:**
Dr. Satyam A. Parmar
Assistant Professor,
Pathology Department,
P.D.U. Medical College, Rajkot (Gujarat), India
E-mail: satyam.parmar@gmail.com

Abstract

Kindler syndrome is a very rare hereditary disorder characterized by acral blister formation in infancy and childhood, progressive poikiloderma, cutaneous atrophy and increased photosensitivity. Since it was first described by Kindler in 1954; less than 100 cases have been reported worldwide. Recently it has been reported that is the first genodermatosis caused by a defect in the actin-extracellular matrix linkage, and the gene was mapped to chromosome 20p12.3. The clinical features of the syndrome have been annotated by different authors but the definite criteria to confirm the diagnosis have not yet been generally accepted.. We report a case that presented to our dermatology department and later on diagnosed as a case of Kindler syndrome at our histopathology department based on clinical as well as on histopathological findings.

Keywords: Kindler syndrome, hereditary disorder

1. Introduction

Kindler syndrome is a rare hereditary disorder characterized by acral blister formation in infancy and childhood, progressive poikiloderma, cutaneous atrophy and increased photosensitivity. The syndrome was originally described by Theresa Kindler[1] in 1954 who proposed that the association of poikiloderma congenitale and hereditary epidermolysis bullosa was not a new disorder but merely the simultaneous occurrence of two rare congenital skin diseases. In 1971, under the designation of hereditary acrokeratotic poikiloderma, Weary *et al*[2] reported a similar disorder with acral blisters in infancy and childhood, widespread eczematous dermatitis, gradual development of diffuse poikiloderma and numerous acral keratoses. Since then approximately 70 cases have been reported, the majority of which have presented similar, overlapping features between Kindler and Weary syndrome. As the molecular and genetic basis of both disorders have remained unknown, for a long time there has been a debate whether Kindler and Weary syndromes are separate clinical entities or belong to the same disease spectrum[3]. Recently it has been reported[4] that the loss of *kindlin-1*, a human homolog of the *Caenorhabditis elegans* actin-extracellular matrix linker protein UNC-112, causes Kindler syndrome and the gene was localized to chromosome 20p12.3[5]. The clinical features of the syndrome have been reviewed by different authors but no definitive criteria for diagnosis have yet been proposed. We report a case of Kindler syndrome that presents a full spectrum of clinical manifestations, and we propose a set of clinical criteria for diagnosis.

2. Case Report

A 48-year-old woman with a history of blister formation, extensive poikiloderma and progressive cutaneous atrophy was admitted to dermatology department. The patient was the 4th uneventful, full-term pregnancy in a family without any history of skin diseases or parental consanguinity. Abnormal blistering tendency was noted soon after delivery. The patient developed trauma-induced acral blisters with clear or hemorrhagic contents that healed without scarring. The blistering tendency, pronounced in infancy and childhood which gradually subsided by the age of 14. Reticular erythema of the face, affecting predominantly the cheeks and spreading progressively to the neck and the upper portions of the chest was noticed within the first years of life. Increased photosensitivity with sunburn after minimal sun exposure and worsening of the condition in summer was present from early infancy.

Dysphagia started at the age of 30 and persisted throughout the years with variable severity. Later in life anal stenosis was suspected. The evolution of the disease lead to the subsequent development of reticular pigmentation, progressive skin atrophy, gingival fragility, webbing of the fingers and the toes, nail dystrophy and ectropion of the lower lids by the age of 40. The formation of circular sclerotic bands around the fingers started at the age of 45 and spread to all the fingers of both hands within 3 years. The physical examination revealed reticular dyschromic patches, atrophic spots, erythema and telangiectasiae all over the face, neck and the upper parts of the chest. Pronounced skin atrophy on the trunk and the extremities with cigarette paper like wrinkling of the skin on the abdomen, dorsum of the hands and feet was present. Syndactyly of the fingers and toes was present and most of the nails were dystrophic. Dermatoglyphics were reduced or absent. The most striking feature observed in our patient was the presence of circular sclerotic bands around the fingers of both hands, most severely impairing the 4th finger of the right hand and the 5th finger of both hands. The pseudoainhum formation threatened the self-amputation of the 5th left digit.

There was extensive mucosal involvement. Gingival swelling and bleeding were common and synechiae between the lips and the gums were present. Ophthalmologic evaluation revealed microcyst formation and ectropion of the lower lids. The history of progressive dysphagia was strongly suggestive of esophageal stenosis that was confirmed by X-ray examination. Osteoma of the cranium was another, probably coincidental finding. The blood tests and urinalysis were within normal range.

The histopathological changes were nonspecific and included epidermal atrophy (Fig.1), basal layer vacuolization (Fig.3), capillary dilatation, pigmentary incontinence (Fig. 2, Fig.4) and upper dermal edema. No characteristic ultrastructural features were found after electron microscopy. The patient did not give consent for the performance of genetic analysis. Increased photosensitivity with bullous reaction was

observed 24 hours after testing. Sun protective creams and emollients as well as symptomatic treatment to alleviate the dysphasia were administered. The pseudoainhum of the 5th left finger was treated surgically.

Fig. 1: Kindler Syndrome- Epidermal Atrophy, 10x

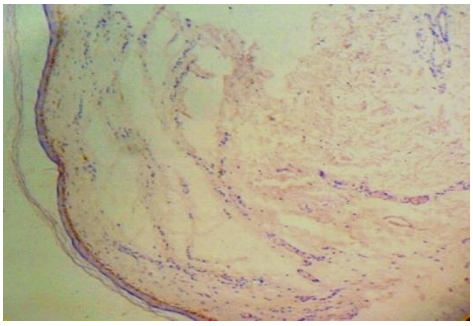


Fig. 2: Kindler Syndrome- Hyperkeratosis, Pigmentary Incontinence, Dermal Edema, 10x

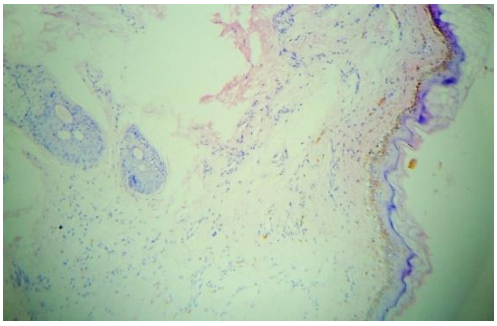


Fig. 3: Kindler Syndrome -Hyperkeratosis With Basal Cell Layer Vacuolization, 40x

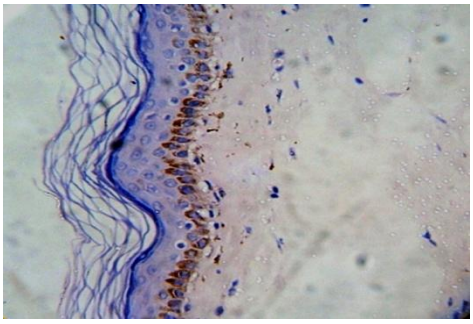
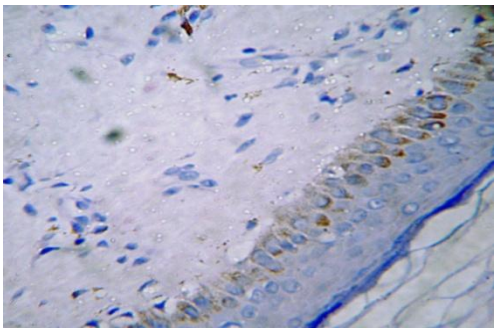


Fig. 4: Kindler Syndrome -Pigmentary Incontinence, 40x



3. Discussion

Less than 100 cases compatible with Kindler's original description have been reported since 1954[6,7,8]. A description of the largest series of patients (26 members of the Ngobe-Bugle tribe residing in isolated villages in rural Panama)[9] has been only recently published.

A detailed study of these reports established that all the patients share the following major clinical findings:

i. Acral blister formation following minor trauma manifested usually at birth or within the first days of life. The blistering tendency gradually subsides and becomes an occasional symptom in adulthood.
ii. Progressive poikiloderma initially manifested and was most pronounced on the lateral aspects of the face and neck.
iii. Diffuse and severe skin atrophy giving "cigarette paper-like" appearance of the skin. These findings are most prominent on the dorsa of the hands and feet and on the abdomen.
iv. Increased photosensitivity with blister formation and sunburn after minimal sun exposure as well as worsening of the condition in summer.

A number of associated findings have been observed in these patients: mucosal involvement with variable severity from gingival fragility and swelling to disabling anal, urethral, esophageal and/or laryngeal stenosis. Syndactyly, sclerotic bands of the wrists[10], nail dystrophy, ectropion of the lower lid, multiple stromal nebular corneal opacities, thickened corneal nerves[11], palmoplantar keratoderma, pseudoainhum, leucokeratosis of the lips and oral mucosa, xerostomia[12], dental caries and atypical periodontitis with earlier onset and more rapid progression[13], squamous cell carcinoma[14], hypohidrosis, phimosis, skeletal abnormalities[15], such as dome-shaped skull, bifid or missing ribs and mandibular abnormalities may be also observed.

Mucosal involvement and webbing of the fingers and the toes have been the most commonly observed "minor" clinical manifestation of the syndrome. Our patient demonstrates the full spectrum of clinical manifestations of Kindler syndrome. In addition, we observed the formation of pseudoainhum extending to all of the fingers of both hands. Pseudoainhum has been observed in patients with Kindler syndrome[16] but none of them experienced such an extensive involvement of the fingers. Osteoma in the spectrum of the syndrome has not been reported so far. No diagnostic ultrastructural features of the syndrome have been described to date[17]. Several reports communicate marked disorganization of the basement membrane with reduplication of lamina densa and cleavage at or close to the dermo-epidermal junction in cases of Kindler syndrome[18,19]. Lanschuetzer *et al*.[20], on the basis of the ultrastructural and immunohistochemical findings in a single patient suggested thatthe syndrome might be primarily an apoptotic disorder of the basal keratinocytes.

The genetic basis of Kindler syndrome was discovered in 2003[21,22]. The gene (*KIND1*) was identified on chromosome 20p12.3. *KIND1* encodes a 677 amino acid protein, *kindlin-1*, a component of focal contacts in keratinocytes expressed in the epidermis and particularly in the basal keratinocytes. Loss of epidermal *kindlin-1* expression results in abnormal skin fragility with defects in actin-extracellular matrix linkage[23]. It is yet unknown whether *kindlin-1* is a merely structural molecule involved in the maintenance of skin integrity or whether it has a regulatory function on other molecules in actin-extracellular matrix adhesion[24]. The pathogenetic link between the loss of *kindlin-1* and the other major clinical findings such as Reticular dyschromic patches, atrophy, erythema and telangiectasia on the face, ectropion and cysts of the lower lids. Skin atrophy and webbing of the fingers. Gingival involvement, photosensitivity and skin atrophy is still unclear.

The differential diagnosis of Kindler syndrome includes a number of rare disorders. Since its description in 1971, hereditary acrokeratotic poikiloderma or Weary syndrome has been the main differential diagnosis of Kindler syndrome and some cases have even been published as Kindler -Weary syndrome[25,26]. However there are significant differences between the manifestation of Kindler and Weary syndrome. Photosensitivity, pronounced in Kindler syndrome, is usually absent in patients with Weary syndrome and blisters are not present shortly after birth but rather appear within the first 6 months of life. Skin atrophy, if present, is not as pronounced as in Kindler syndrome. Widespread dermatitis resembling atopic eczema and keratotic papules on the hands, feet, elbows and knees are features of Weary but not of Kindler

syndrome. Weary syndrome is inherited as an autosomal dominant disorder while the pattern of inheritance of Kindler syndrome is autosomal recessive. Finally, the recent identification of *KIND1* allows a differentiation between the two syndromes on genetic grounds.

Kindler syndrome should be distinguished from hereditary sclerosing poikiloderma[27,28] characterized by progressive poikiloderma notably in the flexural areas, and associated with sclerotic bands, palmar and plantar sclerosis, clubbing of the fingers, poor dentition and calcinosis cutis. The pattern of inheritance is autosomal dominant. Blisters, abnormal photosensitivity, acral keratoses or eczematous dermatitis are not found in hereditary sclerosing poikiloderma.

Rothmund – Thomson syndrome[29] or poikiloderma congenitale, inherited as an autosomal recessive disorder, is characterized by photosensitivity, generalized poikiloderma and a number of associated features:hyperkeratosis of the palms, soles, hands and wrists, sparse fine scalp hair, partial or total alopecia, nail dystrophy, microdontia, hypogonadism, microcephaly and rarely mental retardation. The skin lesions begin as red, edematous plaques and blistering is also possible. Ocular abnormalities such as bilateral cataract, exophthalmus, corneal atrophy, glaucoma and blue sclerae are to be found. Absences of radius, joint contractures, short stature and cystic changes of the long bones have also been described. Kindler syndrome should also be differentiated from the X-linked recessive epidermolysis bullosa simplex[30], xeroderma pigmentosum[31], dyskeratosis congenita[32], and dermatopathia pigmentosa reticularis [33].

To facilitate clinicians in the diagnosis of Kindler syndrome we propose a set of clinical diagnostic criteria:

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, esophageal and laryngeal stenosis

Associated Findings:

- Nail dystrophy
- Ectropion of the lower lid
- Palmoplantar keratoderma
- Pseudoainhum
- Leucokeratosis of the lips
- Squamous cell carcinoma
- Anhidrosis/hypohidrosis
- Skeletal abnormalities
- Poor dentition/dental caries/periodontitis

We consider that the presence of the 4 major criteria makes the diagnosis of Kindler syndrome certain. The presence of 3 major and 2 minor criteria makes the diagnosis probable and the presence of 2 major criteria and 2 minor criteria or associated symptoms renders the diagnosis likely. The proposed criteria provide clinical grounds for the diagnosis and may help clinicians to decide upon the patient's referral for genetic consultation.

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