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

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. The syndrome was originally described by Theresa Kindler 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 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. Recently it has been reported 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. 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.

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 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 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. Recently it has been reported 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. 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 present from early infancy.

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 in our patient was the presence of circular sclerotic bands around the fingers and toes, nail dystrophy and ecchymosis of the fingers started at the age of 45 and spread to all the fingers of both hands within 3 years. The physical examination revealed 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. Recently it has been reported 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. 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.

The evolution of the disease lead to the subsequent development of reticular pigmentation, progressive skin atrophy, gingival fragility, webbing of the fingers and 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 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 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 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 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 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 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 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 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 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 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 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.
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.

3. Discussion

Less than 100 cases compatible with Kindler’s original description have been reported since 19544,7,8. A description of the largest series of patients (26 members of the Ngobe-Bugle tribe residing in isolated villages in rural Panama) 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 hands of the wrists10, nail dystrophy, ectropion of the lower lid, multiple stromal nebular corneal opacities, thickened corneal nerves11, palmpoplantar keratoderma, pseudoainhum, leucokeratosis of the lips and oral mucosa, xerostomia12, dental caries and atypical periodontitis with earlier onset and more rapid progression13, squamous cell carcinoma14, hypohidrosis, phimosis, skeletal abnormalities15, 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 syndrome16 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 date17. 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 syndrome18-20. Langschaetzer et al.20, on the basis of the ultrastructural and immunohistochemical findings in a single patient suggested that the syndrome might be primarily an apoptotic disorder of the basal keratinocytes. The genetic basis of Kindler syndrome was discovered in 200321-22. 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 linkage23. 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 adhesion24. 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 syndrome25,26. 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\textsuperscript{27,28} characterized by progressive poikiloderma notably in the flexural areas, and associated with sclerotic bands, palm 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\textsuperscript{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\textsuperscript{30}, xeroderma pigmentosum\textsuperscript{31}, dyskeratosis congenita\textsuperscript{32}, and dermatopathia pigmentosa reticularis\textsuperscript{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
3. Associated Findings:
   - Nail dystrophy
   - Ectropion
   - Leukokeratosis
   - Gingival fragility and/or swelling
   - Squamous cell carcinoma
   - Anhidrosis/hypohidrosis
   - Skeletal abnormalities
   - Poor dentition/dental caries/pseudodontitis

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.

References

1. Kindler T. Congenital poikiloderma with traumatic bulla formation and progressive cutaneous atrophy. *Br J Dermatol* 1954; 66: 104–11.
2. Weary P, Manley W Jr, Graham G. Hereditary acrokeratotic poikiloderma. *Arch Dermatol* 1971; 103:409–22.
3. Verret J, Avenel M, Larregue M, Panigel-Nguyen C. syndrome de Kindler. *Ann Dermatol Venereol* 1984; 111: 259–69.
4. Siegel D, Ashton G, Penagos H et al. Loss of kindlin-1, a human homolog of the Caenorrhabditis elegans actin-extraacellular-matrix linker protein UNC-112, causes Kindler syndrome. *Am J Human Genet* 2003; 73: 174–87
5. Jobard F, Bouadjar B, Caux F et al. Identification of mutations in a new gene encoding a FERM family protein with a pleckstrin homology domain in Kindler syndrome. *Hum Mol Genet* 2003; 12: 925–35.
6. Patrizi A, Paulizzi P, Neri I et al. Kindler syndrome: report of a case with ultrastructural study and review of the literature. *Pediatr Dermatol* 1996; 13: 397–402.
7. Forman A, Prendiville J, Esterly N et al. Kindler syndrome: report of two cases and review of the literature. *Pediatr Dermatol* 1989; 6: 91–101.
8. Hovnanian A, Blanchet-Bardon C, de Prost Y. Poikiloderma of Theresa Kindler: report of a case with ultrastructural study and review of the literature. *Pediatr Dermatol* 1989; 6: 82–90.
9. Penagos H, Jaen M, Sancho M et al. Kindler syndrome in native Americans from Panama. *Arch Dermatol* 2004; 140: 393–44
10. Al Aboud K, Al Hawsawi K, Al Aboud D, Al Githami A. Kindler syndrome in a Saudi kindred. *Clin Exp Dermatol* 2002; 27: 673–6.
11. Sharma R, Mahajan V, Sharma A. Kindler syndrome. *Int J Dermatol* 2003; 42: 727–32.
12. Chimenos Kustner E, Fernandez Fresquet R, Lopez Lopez J, Rodriguez Rivera Campillo E. Kindler syndrome: a clinical case. *Med Oral* 2003; 8: 38–44.
13. Wiebe C, Penagos H, Luong N et al. Clinical and microbiologic study of periodontitis associated with Kindler syndrome. *J Periodontol* 2003; 74: 25–31.
14. Lotem M, Raben M, Zeltser R et al. Kindler syndrome complicated by squamous cell carcinoma of the hard palate: successful treatment with high-dose radiation therapy and granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2001; 144:1284–6.
15. Sharma R, Mahajan V, Sharma N, Sharma A. Kindler syndrome. *Int J Dermatol* 2003; 42: 727–32.
16. Krunic A, LjiljianaM, Novak A et al. Hereditary acrokeratotic poikiloderma of Weary- Kindler associated with pseudoainhum and sclerotic bands. *Int J Dermatol* 1997; 36: 529–33.
17. Senturk N, Usubutun A, Hashimoto I et al. Kindler syndrome: absence of definite ultrastructural feature. *J Am Acad Dermatol* 1999; 40: 335–7.
18. Shimizu H, Sato M, Ban M et al. Immunohistochemical, ultrastructural and molecular features of Kindler syndrome distinguish it from dystrophic epidermolysis bullosa. *Arch Dermatol* 1997; 133: 7–11.
19. Haber M, Hanna W. Kindler syndrome. Clinical and ultrastructural findings. *Arch Dermatol* 1996; 132: 1487–90.
20. Lanschuetzer C, Mus W, Ebermeier M et al. Characteristic immunohistochemical and ultrastructural findings indicate that Kindler syndrome is an apoptotic skin disorder. *J Cutan Pathol* 2003; 30: 553.
21. Siegel D, Ashton G, Penagos H et al. Loss of kindlin-1, a human homolog of the Caenorhabditis elegans actin-extracellular-matrix linker protein UNC-112, causes Kindler syndrome. *Am J Human Genet* 2003; 73: 174–87.
22. Jobard F, Bouadjar B, Caux F et al. Identification of mutations in a new gene encoding a FERM family protein with a pleckstrin homology domain in Kindler syndrome. *Hum Mol Genet* 2003; 12:925–35.
23. Ashton G. Kindler syndrome. *Clin Exp Dermatol* 2004; 29: 116–21.
24. Ashton G, Irwin Mclean W, South A, Oyama N. Recurrent mutations in kindlin-1, a novel keratinocyte focal contact protein, in the autosomal recessive skin fragility and photosensitivity disorder, Kindler syndrome. *J Invest Dermatol* 2004; 122: 78-83.
25. Kapasi A, Khopkar U, Raj S, Wadhwa S. Weary-Kindler syndrome with multiple seborrheic keratoses. *Int J Dermatol* 1993; 32: 444–5.
26. Wiebe C, Silver J, Larjava S. Early onset periodontitis associated with Weary-Kindler syndrome: a case report. *J Periodontol* 1996; 67: 1004–10.
27. Weary P, Hsu Y, Richardson D et al. Hereditary sclerosing poikiloderma. Report of two families with an unusual and distinctive genodermatosis. *Arch Dermatol* 1969; 100: 413–22.
28. Greer K, Weary P, Nagy R, Robinow M. Hereditary sclerosing poikiloderma. *Int J Dermatol* 1978; 17: 316–22.
29. Wang L, Levy M, Lewis R et al. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. *Am J Med Genet* 2001; 102: 11–7.
30. Francis J. Genetic skin diseases. *Curr Opin Pediatr* 1994; 6: 447–53.
31. Norgauer J, Idzko M, Panther E et al. Xeroderma pigmentosum. Arch Dermatol Venereol 2003; 130:69–73.
32. Dokal I. Dyskeratosis congenita in all its forms. *Br J Haematol* 2000; 110: 768–79.
33. Itin P, Lautenschlager S. Genodermatosis with reticulate, patchy and mottled pigmentation of the neck – a clue to rare dermatologic disorders. *Dermatology* 1998; 197: 281–90.