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Kindler syndrome in a patient with colitis and primary sclerosing cholangitis: coincidence or association?

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Abstract

Kindler syndrome is a rare, autosomal recessive genodermatosis, caused by mutations in the *FERMT1* gene. It is thought to be primarily a skin disease, but other organs may also be involved. We report a case of a novel mutation of *FERMT1* gene in a patient with a probable new phenotype of Kindler syndrome, including colitis and primary sclerosing cholangitis. A 42-year-old man, born to first cousin parents, was referred to our outpatient dermatology clinic with an unknown dermatosis since birth. He presented with neonatal blistering and developed photosensitivity and changes in skin pigmentation during childhood. Since the age of 20, he has had regular follow-up in the gastroenterology clinic, owing to esophageal stenosis, ulcerative colitis, and primary sclerosing cholangitis. Clinical examination revealed jaundice, poikiloderma, diffuse cigarette paper-like atrophy on dorsal surfaces of the hands, and palmoplantar hyperkeratosis. Skin biopsy showed epidermal atrophy covered by orthokeratotic hyperkeratosis. DNA molecular analysis revealed *FERMT1* homozygous mutation c.1179G>A, p.W393X, which has not been reported before. The intestinal phenotype of Kindler syndrome has already been defined previously. However, to the best of our knowledge, no other case of primary sclerosing cholangitis in a patient with Kindler syndrome has been reported.

Keywords: Kindler syndrome, colitis, cholangitis, FERMT1 gene, phenotype.

Introduction

Kindler syndrome (KS), first described by Theresa Kindler in 1954, is a rare, autosomal recessive genodermatosis [1], now classified as a subtype of epidermolysis bullosa [2]. It is caused by loss-of-function mutations in the *FERMT1* (*KIND1*) gene, at chromosomal locus 20p12.3. The *FERMT1* gene encodes the fermitin family homolog 1 (kindlin-1) protein, which is expressed by epithelial cells [1]. To date, more than 70 different mutations of *FERMT1* gene were reported.

KS is typically characterized by trauma-induced blistering, progressive poikiloderma, photosensitivity, and mucosal inflammation [3]. Although KS is considered primarily a skin disease, some reports have shown that other organs may also be involved [3, 4]. Clinical presentation is variable among patients with KS. A genotype-phenotype correlation remains undefined. Different aspects may contribute to the phenotypic diversity, such as genetic, epigenetic, and environmental factors [4]. We report a patient with Kindler syndrome, associated with colitis and cholangitis, in whom a novel mutation of the *FERMT1* gene was identified.

Case Synopsis

A 42-year-old man, born to consanguineous, phenotypically healthy parents, was referred to the outpatient dermatology clinic with a dermatosis

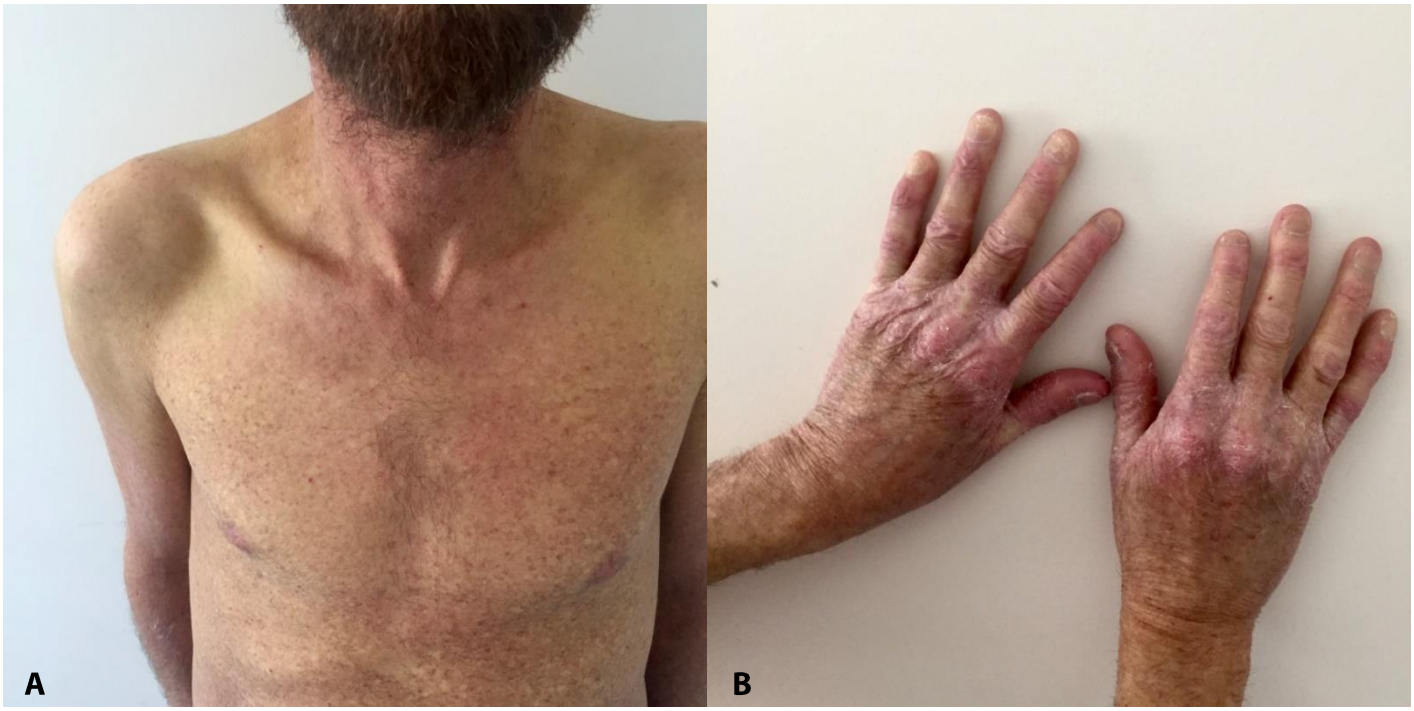

Figure 1. *A) Kindler syndrome. Clinical picture: poikiloderma of the trunk. B) Clinical picture: diffuse cigarette paper-like atrophy on the dorsal surface of the hand.*

since birth, which had been clinically interpreted as epidermolysis bullosa. At birth, he presented with multiple and disseminated blisters and erosions. During childhood, he suffered from photosensitivity and gradually developed changes in skin pigmentation, initially in sun-exposed areas, but subsequently in sun-protected sites as well. Blistering has become less prominent, occurring mainly in trauma-prone areas.

Since the age of 20, his major complaints have been attributable to the gastrointestinal tract and hepatobiliary system and consisted of gingivitis, dysphagia, jaundice, abdominal pain, and hemorrhagic diarrhea. In this context, he has had regular follow-up in the gastroenterology clinic. He has suffered from esophageal stenosis, requiring periodic endoscopic dilation. Routine colonoscopies are suggestive of ulcerative colitis with multiple biopsy samples of colon and rectum demonstrating crypt distortion, an infiltration of the mucosa and submucosa with neutrophils, and the formation of lymphoid aggregates at lamina propria, prominently in the descending colon and rectum. Magnetic resonance cholangiopancreatography exhibited multiple strictures and dilatations of the intrahepatic and extrahepatic biliary ducts. Recently, he had been added to the liver transplant waiting list, as he has developed cirrhosis secondary to cholangitis.

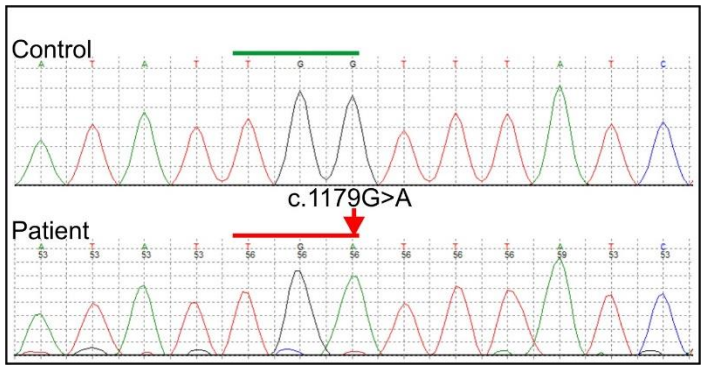

Figure 2. *Kindler syndrome. DNA sequence showing mutation in exon 10, c.1179G>A, p.W393X.*

Dermatological clinical examination revealed jaundice, generalized poikiloderma (**Figure 1**A), diffuse cigarette paper-like atrophy predominantly on dorsal surfaces of the hands (**Figure 1**B) and palmoplantar hyperkeratosis.

Skin biopsy was performed on the abdomen and showed epidermal atrophy and ortokeratosic hyperkeratosis. DNA molecular analysis of the *FERMT1* gene confirmed the diagnosis of Kindler syndrome, revealing a homozygous mutation in exon 10, c.1179G>A, p.W393X (**Figure 2**), which has not been reported.

Case Discussion

Kindlin-1, also known as fermitin family member 1, is an epithelial-specific protein, which belongs to a family of focal adhesion molecules named kindlins, which are involved in actin cytoskeleton and plasma membrane connection and in integrin-mediated cellular processes. Mechanically, kindlin-1 forms molecular complexes with β-integrin and alpha-actinin, and regulates shape, adhesion, migration, and proliferation of epithelial cells [1, 5].

In recent years, the distribution of kindlin-1 has been analyzed in both mice and human tissues. In this context, Zhan et al. concluded that kindlin-1 is highly expressed in human epithelial tissues derived from digestive, respiratory, urogenital, and endocrine systems, in addition to the skin [6].

Kindlin-1 is present throughout the epidermis, particularly in basal keratinocytes. Therefore, kindlin-1 deficiency results in reduced keratinocyte adhesion and proliferation leading to the development of the cutaneous features of KS, which include blistering early in life and subsequent skin atrophy, poikiloderma, keratoderma, and increased predisposition to non-melanoma skin cancer, particularly squamous cell carcinomas [5].

In the colon, kindlin-1 is found throughout the cytoplasm of epithelial cells. Altered expression of kindlin-1 in colonic epithelium may cause epithelial detachment, leading to intestinal barrier disruption, which can be followed by penetration of antigens and ultimately inflammatory bowel disease, [4]. For this reason, patients with KS may present with severe gastrointestinal symptoms, resembling ulcerative colitis [4, 7, 8]. According to published data, about 15% of KS patients exhibit gastrointestinal symptoms [7]. The variability of intestinal manifestations among patients with KS may be explained by partial functional compensation of kindlin-1 deficiency by the intestinal isoform, by the presence of truncated mutant kindlin-1, rather than complete absence of the protein and by environmental factors [4].

To the best of our knowledge, no other case of KS with associated primary sclerosing cholangitis (PSC) has been reported before. The pathogenesis of PSC is not fully understood and seems to be multifactorial [9]. According to the findings of Zhan et al., kindlin-1 is also expressed in the hepatocytes and bile ducts [6]. Cholangiocytes form the epithelia of bile ducts and their tight junctions are important to preserve bile into the duct lumen. A loss of the epithelial barrier function in bile ducts, caused by altered cell adhesion, may lead to regurgitation of bile between cholangiocytes, promoting peribiliary inflammation and fibrosis [9, 10]. This physiopathological mechanism might explain the association between PSC and kindlin-1 deficiency.

Conclusion

Our report illustrates a case of a novel mutation of *FERMT1* gene in a patient with a probable new phenotype of KS, including colitis and PSC. Further studies are necessary to understand the pathophysiological implications of kindlin-1 deficiency in organs other than skin, as well as the genotype-phenotype correlations and the impact of environmental factors in the clinical variability.

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