Kindler Syndrome; New *FERMT-1* Gene Mutation and Breast Cancer Development

Kindler Sendromu; Yeni *FERMT-1* Gen Mutasyonu ve Meme Kanseri Gelişimi

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ABSTRACT Kindler syndrome (KS; OMIM 173650) is a rare autosomal recessive inherited disease characterized by infantile acral bullae, skin atrophy, photosensitivity, chronic inflammation and mucosal stenosis. It is the result of a mutation in the *FERMT-1 (KIND-1)* gene that encodes the fermitin family homologue 1 (FFH1, kindlin-1) protein playing a role in the merging of actin in the basal keratinocytes with the extracellular matrix. More than 40 *FERMT-1* gene mutations have been reported since it was first defined in 1954. Recent studies have postulated that the FFH1 protein plays a regulatory role for the TGFβ signal pathway and can therefore be responsible for the development of breast cancer. We present a 37-year-old female patient with the typical clinical and histopathological features of Kindler syndrome who developed breast cancer during follow-up and where we detected a previously undefined new *FERMT-1* gene mutation.

Key Words: Poikiloderma syndrome of kindler; breast neoplasms; FERMT1 protein, human

ÖZET Kindler sendromu (KS; OMIM 173650) infantil akral büller, deri atrofisi, fotosensitivite, kronik inflamasyon ve mukozal stenoz ile karakterize nadir görülen otozomal resesif kalıtsal bir hastalıktır. Kindler sendromu bazal keratinositlerdeki aktin ile ekstrasellüler matriks arasındaki birleşmede rol alan fermitin family homologue 1 (FFH1, kindlin-1) proteinini kodlayan *FERMT-1 (KIND-1)* genindeki mutasyon sonucu oluşmaktadır. Tanımlandığı 1954'den bu yana 40'dan fazla *FERMT-1* gen mutasyonu bildirilmiştir. Yakın zamanda yapılan çalışmalarda FFH1 proteinin TGFβ sinyal yolağında düzenleyici rol oynadığı ve bu yolak üzerinden meme kanseri gelişiminden sorumlu olabileceği öne sürülmüştür. Burada Kindler sendromunun tipik klinik ve histopatolojik özelliklerini gösteren, daha önce tanımlanmamış yeni *FERMT-1* gen mutasyonu saptadığımız ve takipte meme kanseri gelişen 37 yaşında bir kadın olgu sunulmaktadır.

Anahtar Kelimeler: Poikiloderma kindler sendromu; meme tümörleri; FERMT1 protein, insan

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Kindler syndrome is a rare genetic disease characterized by congenital acral bullae, photosensitivity, poikiloderma and skin atrophy.[1] The inheritance is usually autosomal recessive but autosomal dominant and sporadic cases have also been reported.[2] The syndrome is the result of a mutation in the *FERMT-1* gene that encodes the FFH1 protein playing a role in the merging of actin in the basal keratinocytes with the extracellular matrix.[3,4] Although the possible role of the FFH1 protein in cancer development is still not clear, recent studies have postulated it has an important role in breast cancer development and lung metastasis due to breast cancer.[5]

CASE REPORT

A 37-year-old female presented at our outpatient clinic with redness of the face and neck, skin thinning, color change in the body, and hardness of the hands and feet. The patient's symptoms started post-partum as bullae in the hands and feet and she was diagnosed with hereditary epidermolysis bullosa. She then gradually developed redness of the face, neck, forearm, hands and feet, skin thinning, hardness of the fingers and toes, and color changes in various parts of her body. She had been diagnosed with scleroderma due to the widespread sclerosis of the fingers and toes and the patient had undergone extensive investigation for systemic involvement by scleroderma.

Her parents were first-degree relatives, however there was no similar family history. She complained of photosensitivity and the dermatology examination revealed widespread poikiloderma of the face and neck; general skin atrophy that was most prominent in the hands and feet, xerosis, scleroatrophy of the fingers, patchy hypopigmented and hyperpigmented macules on the body and extremities, ectropion of the lower eyelid, and gingivitis (Figures 1-3). The other systems were within normal limits on examination.

The hemogram, routine biochemistry and urinalysis results were normal. ANA and anti-dsDNA were negative.

Histopathological examination of the skin samples taken from the neck and face showed epidermal atrophy, vacuolization of the dermoepidermal junction, and increased perivascular lymphocytes and melanophages in the dermis (Figure 4). Electron microscopy could not performed.

Following informed consent, tissue and blood samples were obtained for genetic analysis. The genetic analysis revealed a previously undefined *FERMT-1* gene mutation at the c.1209C>G, p.Y403X locus that showed a homozygous pattern in the patient and heterozygous pattern in the father and two siblings. The mother is deceased. The patient was diagnosed with Kindler syndrome with these clinical, histopathological and genetic findings.

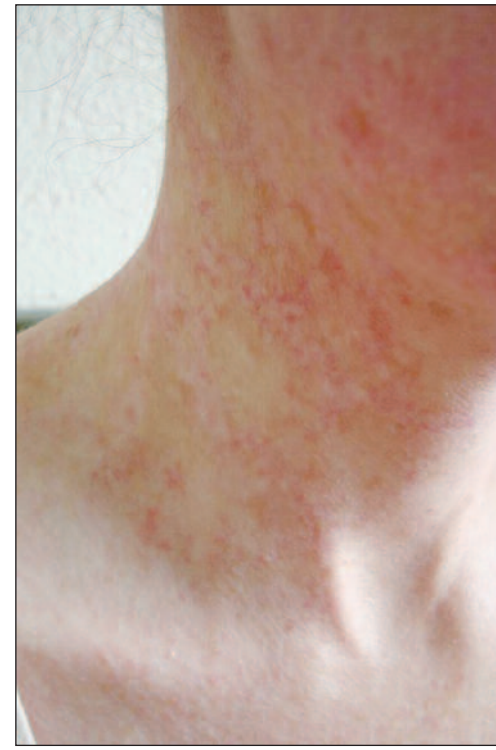

FIGURE 1: Widespread poikiloderma of the neck.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

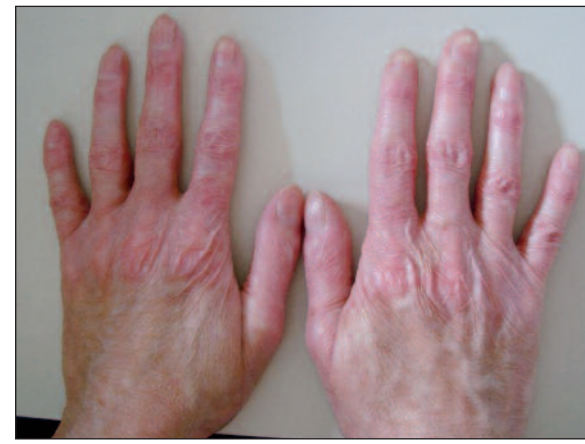

FIGURE 2: Marked skin atrophy on dorsal aspects of hands, hardness of the fingers.
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

She was provided information on sunlight protection and possible complications. One year later, she presented with a painful mass in both breasts. The breast examination revealed multiple solid masses with the largest 1 cm in diameter in the left breast and 2.5 cm in diameter in the right breast. She was referred to the general surgery department. The biopsy material obtained from both breasts revealed

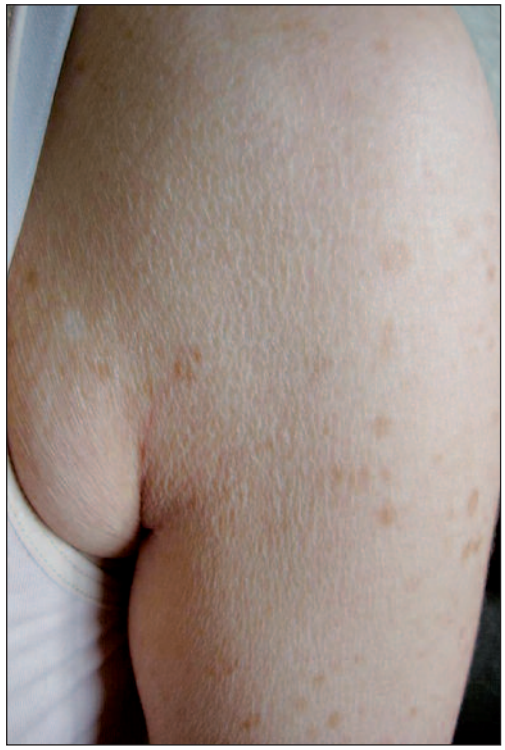

FIGURE 3: Patchy hypopigmented and hyperpigmented macules and xerosis on the upper extremities.
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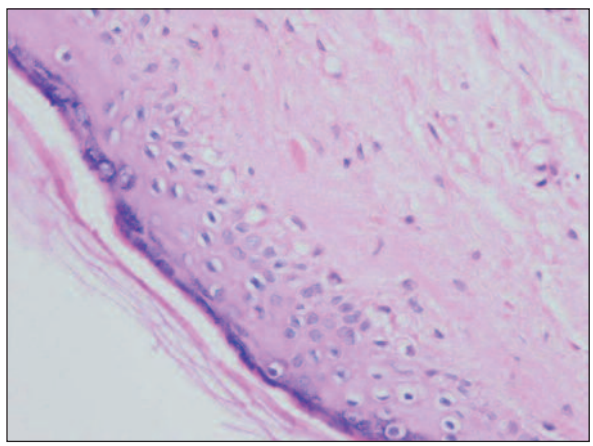

FIGURE 4: Epidermal atrophy, vacuolization of the dermoepidermal junction, and increased perivascular lymphocytes on histopathological examination (HE x200 magnification).
(See for colored form http://dermatoloji.turkiyeklinikleri.com/)

infiltrative ductal cancer, grade 2/3, on histopathological examination and the patient underwent bilateral mastectomy then received chemotherapy and radiotherapy for a year. There was no metastasis within a year status post treatment. She continues to be followed-up for her metastasis risk.

DISCUSSION

Kindler syndrome is a rare genodermatosis where signs of hereditary epidermolysis bullosa and congenital poikiloderma are seen together.[2] The syndrome appears as acral bullae in the early infantile period while photosensitivity and progressive poikiloderma develop later on.[6,7] Other signs include gingival fragility, periodontitis, tooth loss, oral-intestinal-urethral mucosa involvement, ectropion, palmoplantar hyperkeratosis, nail dystrophy, sclerodactyly, webbing of the fingers and toes, and hypo-or anhydrosis.[8,9]

Kindler syndrome develops as a result of mutations in the *FERMT-1* gene located at the short arm of chromosome 20 that encodes the FFH1 protein.[10-13] The FFH1 protein plays an important role in integrin functions such as epidermal cell motility, cell adhesion, proliferation and polarization.[14] Increased fragility and atrophy are seen in epithelial cells with the loss of FFH1 function. Close to 100 Kindler syndrome patients and more than 40 *FERMT-1* gene mutations have been reported so far.[15] In contrast to the other bullous genodermatoses, genetic analysis is very important for the early diagnosis of Kindler syndrome.[16] The discovery of the gene mutation helps confirmation of the diagnosis in new cases. Therefore we obtained the case's tissue and blood samples and her family's blood samples for genetic analysis. The genetic analysis revealed a previously undefined *FERMT-1* gene mutation.

In addition to the clinical and genetic findings of Kindler syndrome, the histopathological findings are also important. Light microscopy examination of the poikilodermic skin reveals orthokeratotic hyperkeratosis, epidermal atrophy, focal vacuolization of the basal layer, multiple melanophages in the papillary dermis and rarely colloid bodies.[17] Vascular ectasia and lymphohistiocytic infiltration can also be present. The most prominent finding on electron microscopy is the separation between the basal lamina and keratinocyte cell membrane together with basal lamina reduplication. It is also possible to see wide bands with a reticular staining pattern at the dermoepidermal junction using antibodies against type 4 and 7 collagen.[18] However, the histologic findings and ultrastructural features are

not specific and have not been well described to date.[19]

At present, there is no curative treatment model for Kindler syndrome. The patients should be informed about sun protection, due to the increased mucocutaneous malignancy risk with advancing years.[8] Surgical treatment is recommended for stenotic complications that may develop with gastrointestinal and urinary mucosa involvement.[18]

Recent studies have also demonstrated an increased risk of mucocutaneous cancer, breast cancer and solid organ breast cancer metastasis in Kindler syndrome patients.[5,6,10] At present, 5 patients were reported to have cutaneous squamous cell carcinomas among Kindler syndrome patients.[20] Photosensitivity, ultraviolet radiation exposure and trauma may increase the rate of epithelial cancers.[21] Although patients with Kindler syndrome have a high propensity to develop cutaneous squamous cell carcinomas, the role of kindlin-1 in epithelial carcinogenesis is not known and needs further investigation. The studies on the association between Kindler syndrome and cancer development have found that proteins from the fermitin family bind directly to β integrins, and that β1 integrin activation is inhibited with FFH1 deficiency, leading to disturbed cell adhesion, proliferation, polarity and motility and thus contributing to cancer development. FFH1 is overexpressed in various carcinomas but its relevance remains unknown.[5] It is an open question whether there is an association between Kindler syndrome and breast cancer as there is no case report in this regard in the current literature. In this case well known genetic risk factors of breast cancer have not been excluded. Nevertheless, it is remarkable to have shown a previously undefined homozygous pattern of *FERMT-1* gene mutation at the c.1209C>G, p.Y403X locus and further exploration may provide clues for better diagnostic and therapeutic interventions.

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