Epidermodysplasia Verruciformis (EV) is an autosomal recessive disorder characterized by abnormalities of immune response against human papilloma virus (HPV).\textsuperscript{1,2} It is manifested as polymorphic cutaneous lesions, including pityriasis versicolor like macules and flat wart-like papules that usually appear on the face, trunk, and extremities in childhood and cutaneous malignancies on sun-exposed areas in adulthood.\textsuperscript{1-4} Ichthyosis vulgaris is a common keratinization disorder caused by mutations in the filaggrin gene (FLG). It is characterized by wide-spread xerosis and ichthyosiform scales.\textsuperscript{5} Becker nevus is a benign cutaneous hamartoma that presents as both hypermelanosis and hypertrichosis usually localized unilaterally on upper extremities and trunk.\textsuperscript{6} Nevus spilus is a pigmented...
skin lesion on trunk and extremities, consisting of a large, light tan patch, containing macules or papules.7

Herein, we present a 36 years old male diagnosed with four dermatological diseases: EV, ichthyosis vulgaris, nevus spilus and Becker nevus.

**CASE REPORT**

A 36-year-old male patient referred to our clinic with a histopathological report of well-differentiated squamous cell carcinoma excised from his frontal region. He had 15 years history of pigmented papules on both hands and face, xerosis and scaling on extremities especially in the winter. On his family history he reported pigmented papules on his mother’s hands. His past medical history was unremarkable.

Dermatological examination revealed multiple, erythematous, scaling macules on frontal region of the face and multiple verrucous papules on the dorsum of hands (Figure 1), and brownish ichthyosiform scaling patches on both upper and lower legs (Figure 2 a, b). We also observed macular hyperpigmentation and hypertrichosis on the right thoracic region suggesting diagnosis of Becker nevus (Figure 3) and light-brown patch, speckled with multiple darker macules under the left scapula which indicates nevus spilus (Figure 4).

Histopathological examination of the punch biopsy obtained from the right leg revealed ortho hyperkeratosis, atrophic changes in epidermis, thinning of granular layer, which were consistent with the diagnosis of ichthyosis vulgaris. The patient was diagnosed EV based on biopsy taken from lesions on dorsum of his right hand while excisional biopsy from frontal region revealed actinic keratosis with severe dysplasia.

Systemic acitretin (10 mg/day) and urea containing emollient treatments were started and actinic keratosis was treated by cryotherapy with two weeks intervals. Subsequently ichthyotic scaling on the legs and EV lesions on the both hands regressed.

Genetic analysis of blood sample of the patient with provisional diagnosis of ichthyosis vulgaris revealed p.Arg573 Trp missense mutation in transglutaminase 1 (TGM1) gene and the patient was evaluated as the carrier for the relevant mutation. When the blood samples of the patient and his family were examined for EV, no mutation was found in EVER 1 (TCM6) gene. However, genetic
analysis revealed homozygous mutation of EVER 2 (TCM8) gene in the patient and his father and heterozygote mutation in his mother and brother. The homozygous mutation detected in his father did not related with clinical findings, so it was evaluated as polymorphism.

**DISCUSSION**

Epidermodysplasia verruciformis (EV) is a rare genodermatosis which is first described by Lewandowsky and Lutz in 1922. It is believed that inactivating mutations of EVER1 and EVER2 genes located on chromosome 17 may lead to down regulation of cell-mediated immunity to approximately 20 subtypes of HPV.1,3,4 Akgül et al. presented a 22-year-old male patient and his mother with seborrheic keratosis-like viral warts histopathologically consistent with EV. However, genetic analysis detected no mutations of the EVER1 and EVER2 genes in these patients.8 Verruca plana-like lesions are associated with HPV-3 and 10; while squamous cell carcinoma (SCC) and Bowen disease are associated with HPV-5 and 8.1,3,4,9 The malignant transformation of EV lesions to SCC occurs in 30-70% of the cases. Early identification and appropriate treatment of actinic keratoses is also important as they lead to invasive SCC.3

Our patient had a history of well differentiated SCC and the excised lesion on his hand was compatible with actinic keratosis with severe dysplasia. Tsurumi et al reported a 23-years old male diagnosed with congenital combined deficiency of factor V and factor VIII, acquired ichthyosis and EV. They suggested that immunological defects in this patient may be related with EV.10

Icthyosis vulgaris, is an autosomal dominant genodermatosis characterized by the deficiency of filaggrin and profilaggrin in keratohyalin granules. Histopathologically; orthohyperkeratosis, diminished to absent stratum granulosum and decreased or absent keratohyalin granules may be observed.5

Mutations in the TGM1 gene were considered to be the most prevalent cause of the autosomal recessive congenital ichthyosis.11 Patients with congenital ichthyosiform erythroderma and lamellar ichthyosis are more susceptible to develop skin malignancies, and Natsuga et al. reported that the risk of development of SCC is increased in patients with autosomal recessive ichthyosis with TGM-1 mutation.12,13 Curth and Macklin presented a patient with ichthyosis hystrix and congenital ichthyosiform erythroderma in whom the skin biopsy of the patient revealed features reminiscent of EV.14 In our presented case, clinical and histopathological examinations were consistent with ichthyosis vulgaris, however missense mutation in TGM1 gene was present.

Andersen et al. suggested that homozygous FLG mutations could contribute to the susceptibility of AK in patients with ichthyosis vulgaris, which is considered as an important risk factor for SCC.15 We did not detect FLG mutation in our patient; therefore the development of SCC was attributed to EV in this particular case.

Coincidence some of these dermatological diseases were also reported in the literature. Criscione et al. presented an 18-years old male patient with a large, scaly Becker nevus plaque on his right thigh. The histopathologic features of that lesion was consistent with ichthyosis vulgaris.6 The Becker nevus of our patient did not have ichthyosiform features. On the other hand, Crosti et al. reported a 16-years old male patient with nevus spilus on his back in addition to ichthyosis vulgaris. His family history revealed ichthyosis and nevus spilus in his grand-
father. Our case’s genetical examination showed that he was autosomal recessive form of ichthyosis vulgaris; but nevus spilus and Becker nevus were not observed in his family history.

In conclusion, to our knowledge, this is first reported case of concomitant EV with ichthyosis vulgaris, Becker nevus and nevus spilus. It is not clear whether these four dermatological diseases in the same patient are on somehow related to each other or just a matter of coincidence. Further case reports and studies are warranted to clarify there is a common genetic pathogenic process behind all these lesions.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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