OLGU SUNUMU CASE REPORT

DOI: 10.5336/dermato.2019-70175

Four Dermatological Diseases in a Patient: Is it an Association or Just a Coincidence?

Bir Olgu, Dört Dermatolojik Hastalık: Rastlantı mı, Birliktelik mi?

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This case report was presented as a poster at XXIII. Prof. Dr. A. Lütfü Tat Symposium, 22-26 Nov 2017, Ankara, Turkey.

ABSTRACT Epidermodisplasia verruciformis (EV) is a rare, inherited disease. The disease occurs with human papilloma virus (HPV), which has more than 70 types. Patients have a high risk of developing skin malignancies on sun-exposed areas. Ichthyosis vulgaris is an autosomal dominant inherited skin disorder and characterized by diffuse scaling. Becker nevus is a benign cutaneous hamartoma that presents as both hypermelanosis and hypertrichosis. Nevus spilus is an epidermal nevus consisting of a light tan patch with numerous dark brown macules and papules. Coincidence of some of the dermatological diseases were reported in the literature. However, the concurrent occurrence of EV with ichthyosis vulgaris, Becker nevus and nevus spilus has not been previously reported. Herein, we present a 36 years old male diagnosed with four dermatological diseases: EV, ichthyosis vulgaris, nevus spilus and Becker nevus.

Keywords: Epidermodisplasia verruciformis; ichthyosis vulgaris; papillomavirus infections; becker nevus; nevus spilus

ÖZET Epidermodisplazya verrüsiformis (EV) nadir görülen, herediter bir hastalıktır. Etkeni 70'ten fazla tipe sahip olan human papilloma virüstür (HPV). Bu hastalar güneş gören alanlarda kütanöz malignite gelişimi açısından yüksek riske sahiptirler. İktiyozis vulgaris, otozomal dominant geçişli kalıtsal bir deri hastalığıdır ve yaygın pullanma ile karakterizedir. Becker nevüs hiperpigmentasyon ve hipertrikozun bir arada görüldüğü, benin kütanöz hamartomatöz lezyondur. Nevüs spilus, koyu renkli makül ve papüller içeren açık renkli yama tarzında lezyondan oluşan bir epidermal nevüstür. Literatürde bazı dermatolojik hastalıkların birlikteliği bilinmektedir. Ancak, EV, iktiyozis vulgaris, Becker nevüs ve nevüs spilus birlikteliği henüz bildirilmemiştir. Burada EV, iktiyozis vulgaris, nevüs spilus ve Becker nevüs birlikteliği olan 36 yaşında bir erkek hasta sunulmaktadır.

Anahtar Kelimeler: Epidermodisplazya verrüsiformis; iktiyozis vulgaris; papillomavirüs enfeksiyonları; becker nevus; nevüs spilus

Epidermodysplasia verruciformis (EV) is an autosomal recessive disorder characterized by abnormalities of immune response against human papilloma virus (HPV).[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.[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.[5] Becker nevus is a benign cutaneous hamartoma that presents as both hypermelanosis and hypertrichosis usually localized unilaterally on upper extremities and trunk.[6] Nevus spilus is a pigmented skin lesion on trunk and extremities, consisting of a large, light tan patch, containing macules or papules.[7]

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Peer review under responsibility of Turkiye Klinikleri Journal of Dermatology.

Received: 26 Jul 2019 ***Received in revised form:*** 18 Nov 2019 ***Accepted:*** 19 Nov 2019 ***Available online:*** 24 Dec 2020

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 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 2a, 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).

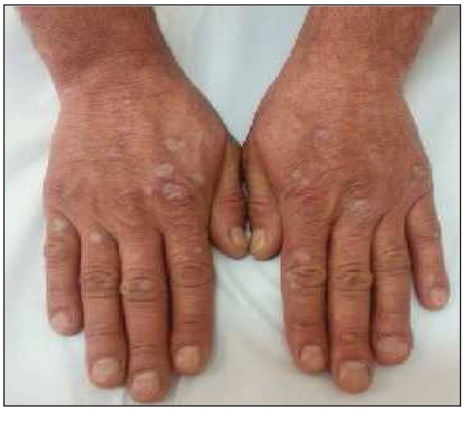

FIGURE 1: Multiple, confluent, verrucous papules and plaques on the dorsum of hands suggesting epidermodysplasia verruciformis.

Histopathological examination of the punch biopsy obtained from the right leg revealed orthohyperkeratosis, atrophic changes in epidermis, thinning of granular layer, which were consistent with the diagnosis of ichthyosis vulgaris. The patient was diagnosed with EV based on biopsy taken from the 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 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)

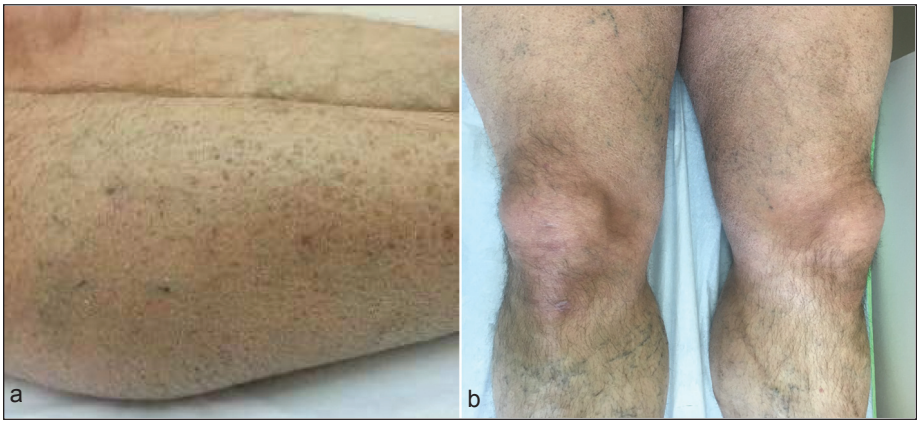

FIGURE 2: Brownish, flaky, ichthyosiform scaling patches on the lateral aspect of legs (a) and the medial aspect of both thighs (b) suggesting ichthyosis vulgaris.

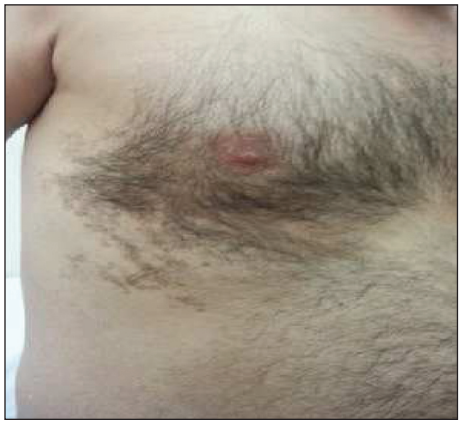

FIGURE 3: A 10×5 cm sized, macular hyperpigmentation and hypertrichosis with irregular border on the right thoracic region suggesting Becker nevus.

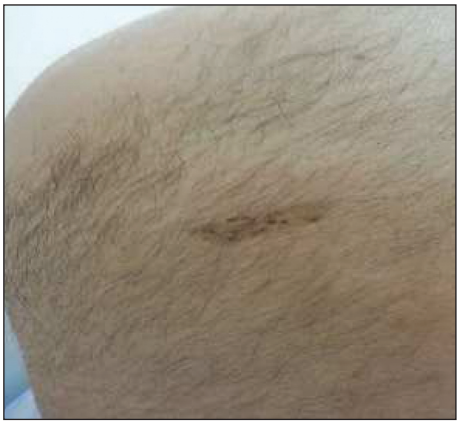

FIGURE 4: A 5×2 cm sized, light-brown patch, speckled with multiple darker macules under the left scapula suggesting nevus spilus.

gene in the patient and his father and heterozygote mutation in his mother and brother. The homozygous mutation detected in his father was 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 EVER 1 and EVER 2 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]

Ichthyosis 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 TGM1 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 of 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 grandfather.[7] 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 the 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.

Informed consent form was obtained for this case report.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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

Idea/Concept: *Hilal Kaya Erdoğan, Esra Ağaoğlu;* ***Design:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu;* ***Control/Supervision:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu;* ***Data Collection and/or Processing:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu;* ***Analysis and/or Interpretation:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu;* ***Literature Review:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu;* ***Writing the Article:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu;* ***Critical Review:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu;* ***References and Fundings:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu;* ***Materials:*** *Hilal Kaya Erdoğan, Esra Ağaoğlu; Ersoy Acer, Zeynep Nurhan Saraçoğlu.*

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