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FIGURE 1. Clinical features of epidermodysplasia verruciformis. A, Neck and (B) right upper arm showing hypopigmented macular lesions resembling tinea versicolor (→).

was performed using single-step polymerase chain reaction followed by reverse line blot (Ampliquality HPV-Type Express v3.0, AB Analitica, Padova, Italy), which is able to detect 40 HPV genotypes and universal HPV. Of 40 HPV type tested (HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42–45, 51–59, 61, 62, 64, 66, 67, 68 (68a e 68b), 69–73, 81–84, 87, 89, and 90), the presence of HPV 6 was detected.

DISCUSSION

The age at which the patient was diagnosed with epidermodysplasia verruciformis (EV) lesions, the history of SLE, and 3 years of immunosuppressive treatment imply the diagnosis of acquired EV in our patient. The negative family history for EV also suggests sporadic rather than inherited EV, although autosomal recessive disease can of course manifest as single cases in a family. As mentioned above, the age at diagnosis in our patient matches the sporadic type, whereas hereditary EV usually occurs in childhood or early

adolescence.¹¹ However, 1 study reported the occurrence of nonclassic genetic EV in an adult with a germline *ITK* mutation.¹² This patient also has T-Cell lymphoma diagnosed 7 years before the EV. In general, nonclassic genetic EV is suggested to associate with certain concomitant diseases.⁸ These diseases include Burkitt lymphoma, bronchopulmonary diseases (*RHOH* mutation),⁴ flat warts, EBV infection, oral candidiasis (*MST1* mutation),⁷ molluscum contagiosum, herpetic ulcers, granulomatous tuberculoid leprosy (*CORO1A* mutation),⁶ and lipoid proteinosis (*ECM1* mutation).⁵ However, SLE is not among the concomitant disorders reported so far in nonclassic genetic EV.

Several observations support the notion that HPV infection, and subsequently EV, developed in our patient as a complication of SLE and/or its treatment. EV has been reported in patients receiving azathioprine as a treatment for their SLE.^{13–15} It was suggested that the immunosuppressive effect of azathioprine can facilitate HPV infection and thereby development of EV in patients with SLE.¹³ Although our patient did not receive azathioprine, she has been receiving the immunosuppressant methylprednisolone with doses of 8 mg/d for 3 years before her EV diagnosis. The administration of methylprednisolone over 7.5 mg–10 mg/d has been suggested as an infection risk factor in patients with SLE.¹⁶ In addition, SLE itself also results in impaired cell immunity mainly through the reduction of T-cell number and T-cell activity.¹⁷

To the best of our knowledge, our report is the first of HPV type 6 in EV. HPV 6 is known as mucosal, low-risk HPV¹⁸ and traditionally regarded as being only weakly associated with cancer.¹⁹ The notion of only low malignant potential of HPV 6 has been supported by the observation in an in vitro study of low expression of its E7 protein, which decreases the ability of HPV 6 to immortalize human keratinocytes.²⁰ However, through other studies, HPV 6 has been identified alone, or combined with other HPV types, in significant percentages of cutaneous SCC cases in 16.2%,²¹ 20%,²² and 23%,²³ respectively. Thus, the association between HPV 6 and malignancy needs to be further explored.

FIGURE 2. Microscopic features of epidermodysplasia verruciformis. Skin biopsy from the right lower arm was submitted to H&E stain. A, ×100 and (B) ×400 magnification views of epidermis showing keratohyalin granules (→) and keratinocyte with larger cell size and blue–grey pallor cytoplasm (▶). The same paraffin block was submitted to immunohistochemistry for assessment of p16 expression. C, ×400 magnification views of parabasal cells showing immunoreactivity to p16 (Δ).

Because we need to consider the possible cancer risk increase in patients with HPV 6 EV, we decided on 2 follow-up plans to address this concern in our patient. The first plan aims to restore the immune response through immunosuppressive treatment modification guided by SLE progression monitoring.^{24,25} The second plan aims to recognize early signs of SCC development or other HPV-related cutaneous lesions.²⁶ A monthly follow-up plan has been assigned to the patient. The latest follow-up of our patient showed minimal SLE manifestations and improved EV lesions using a dose of 4 mg/d methylprednisolone during 3 consecutive days monthly.

CONCLUSION

We report a case of acquired EV in a patient with SLE and 3 years of immunosuppressive methylprednisolone treatment. The biopsy from EV lesion showed characteristics of HPV infected keratinocytes, immunoreactivity to p16, and the presence of HPV 6 which type has not been reported previously in EV. Although HPV 6 is traditionally regarded as belonging to the low-risk HPV group, some reports have identified its presence in significant percentages of cutaneous SCC. Therefore, as long as cancer risk in HPV 6 EV is unclear, we propose, a continuous clinical follow-up of the EV lesions in these patients to detect early signs of malignant transformation.

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REFERENCES

- Przybyszewska J, Zlotogorski A, Ramot Y. Re-evaluation of epidermodysplasia verruciformis: reconciling more than 90 years of debate. *J Am Acad Dermatol*. 2017;76:1161–1175.
- Orth G. Genetics of epidermodysplasia verruciformis: insights into host defense against papillomaviruses. *Semin Immunol*. 2006;18:362–374.
- Lazarczyk M, Pons C, Mendoza JA, et al. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. *J Exp Med*. 2008;205:35–42.
- Crequer A, Troeger A, Patin E, et al. Human RHOH deficiency causes T cell defects and susceptibility to EV-HPV infections. *J Clin Invest*. 2012;122:3239–3247.
- O'Blencs C, Pasternak S, Issekutz A, et al. Epidermodysplasia verruciformis in lipoid proteinosis: case report and discussion of pathophysiology. *Pediatr Dermatol*. 2015;32:118–121.
- Stray-Pedersen A, Jouanguy E, Crequer A, et al. Compound heterozygous CORO1A mutations in siblings with a mucocutaneous-immunodeficiency syndrome of epidermodysplasia verruciformis-HPV, molluscum contagiosum and granulomatous tuberculoid leprosy. *J Clin Immunol*. 2014;34:871–890.
- Crequer A, Picard C, Patin E, et al. Inherited MST1 deficiency underlies susceptibility to EV-HPV infections. *PLoS One*. 2012;7:e44010.
- Huang S, Wu JH, Lewis DJ, et al. A novel approach to the classification of epidermodysplasia verruciformis. *Int J Dermatol*. 2018;57:1344–1350.
- Rogers HD, Macgregor JL, Nord KM, et al. Acquired epidermodysplasia verruciformis. *J Am Acad Dermatol*. 2009;60:315–320.
- Nuovo G, Nicol A, de Andrade CV, et al. New biomarkers of human papillomavirus infection in epidermodysplasia verruciformis. *Ann Diagn Pathol*. 2019;40:81–87.
- Cubie HA. Diseases associated with human papillomavirus infection. *Virology*. 2013;445:21–34.
- Fouere S, Aubin F, Pere H, et al. Epidermodysplasia verruciformis in an adult patient with a germline Interleukin-2 inducible T-Cell Kinase mutation and lymphoma: the case of inherited versus acquired. *J Eur Acad Dermatol Venereol*. 2018;32:e240–e241.
- Holmes C, Chong AH, Tabrizi SN, et al. Epidermodysplasia verruciformis-like syndrome in association with systemic lupus erythematosus. *Australas J Dermatol*. 2009;50:44–47.
- Garcia-Rio I, Garcia FVMJ, Dauden E, et al. Epidermodysplasia verruciformis-like lesions in a patient with systemic lupus erythematosus. *Acta Derm Venereol*. 2003;83:229–230.
- Tanigaki T, Kanda R, Sato K. Epidermodysplasia verruciformis (L-L, 1922) in a patient with systemic lupus erythematosus. *Arch Dermatol Res*. 1986;278:247–248.
- Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus* 2013; 22:1286–1294.
- Andrianakos AA, Tsiachlis PN, Merikas EG, et al. Cell-mediated immunity in systemic lupus erythematosus. *Clin Exp Immunol*. 1977;30:89–96.
- Loenenbach AD, Poethko-Muller C, Pawlita M, et al. Mucosal and cutaneous Human Papillomavirus seroprevalence among adults in the prevaccine era in Germany—results from a nationwide population-based survey. *Int J Infect Dis*. 2019;83:3–11.
- Faust H, Andersson K, Luostarinen T, et al. Cutaneous human papillomaviruses and squamous cell carcinoma of the skin: nested case-control study. *Cancer Epidemiol Biomarkers Prev*. 2016;25:721–724.
- Barbosa MS, Vass WC, Lowy DR, et al. In vitro biological activities of the E6 and E7 genes vary among human papillomaviruses of different oncogenic potential. *J Virol*. 1991;65:292–298.
- Shahmahmoudi S, Mahmoudi M, Azad TM, et al. Prevalence of mucosal types of human papillomavirus in skin lesions in north part of Iran. *Cancer Lett*. 2007;247:72–76.
- Shayanfar N, Hosseini N, Panahi M, et al. Detection of mucosal type human papillomavirus in cutaneous squamous cell carcinoma in Iran. *Pathol Res Pract*. 2013;209:90–94.
- Hama N, Ohtsuka T, Yamazaki S. Detection of mucosal human papilloma virus DNA in bowenoid papulosis, Bowen's disease and squamous cell carcinoma of the skin. *J Dermatol*. 2006;33:331–337.
- Lecapitaine AL, Perronne V, Granier F. Remission of an epidermodysplasia verruciformis-like eruption in an HIV-positive man long after immune restoration. *Eur J Dermatol*. 2015;25:488–490.
- Ovits CG, Amin BD, Halverstam C. Acquired epidermodysplasia verruciformis and its relationship to immunosuppressive therapy: report of a case and review of the literature. *J Drugs Dermatol*. 2017;16:701–704.
- Majewski S, Jablonska S. Human papillomavirus-associated tumors of the skin and mucosa. *J Am Acad Dermatol*. 1997;36(5 pt 1):659–685; quiz 686–658.