

# Epidermodysplasia Verruciformis Associated with Plasmablastic Lymphoma and Hepatitis B Virus Infection

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**SUMMARY** Epidermodysplasia verruciformis is a rare genodermatosis characterized by inherited susceptibility to infection with certain papillomaviruses, which leads to the development of disseminated plane wart-like lesions. In some patients, lesions resembling pityriasis versicolor appear. Epidermodysplasia verruciformis has also been reported in immunosuppressed patients, most notably those with HIV infection. The affected patients are predisposed to development of skin and mucosal malignancies. We describe the rare occurrence of plasmablastic lymphoma in a patient with long lasting epidermodysplasia verruciformis and hepatitis B virus infection.

**KEY WORDS:** epidermodysplasia verruciformis, human papillomavirus infection, hepatitis B virus infection, plasmablastic lymphoma

## INTRODUCTION

Epidermodysplasia verruciformis (EV) is a rare disorder with an increased susceptibility to human papillomavirus (HPV) infection affecting the skin (1,2). Early development of widespread, refractory flat warts and pityriasis versicolor-like lesions are unique features. EV may occur in either as hereditary trait or in association with various acquired immunodeficiencies, particularly HIV infection (3-5). Non-melanoma skin cancers develop in over one-third of cases (6). There

are few reports of hematologic malignancies associated with EV (7,8). We present the rare occurrence of plasmablastic lymphoma in a patient with long lasting EV and hepatitis B virus (HBV) infection.

## CASE REPORT

A 27-year-old man presented with dyspnea and hoarseness of two-week duration, which were pro-

gressing to develop stridor. On physical examination, long lasting diffuse skin lesions with different characteristics were noticed.

The skin lesions included scattered light and dark brown papules resembling plane warts on the face, upper trunk and proximal aspect of upper extremities, which had appeared from childhood (Fig. 1).

The skin of the lower trunk and the neck revealed extensive, mildly pruritic eczematous lesions that had developed during adolescence. The skin of the dorsal aspect of the hands showed discrete dark pink plane polygonal papules masquerading lichen planus lesions, but were not pruritic. They had been present and remained unchanged for two years and were not responsive to topical corticosteroids.

Examination of the pubic and genital skin detected numerous umbilicated flesh-colored 0.5×0.5 cm papules, which were diagnosed as molluscum contagiosum (Fig. 2).

Family history indicated that his brother had been infected with HBV through a blood transfusion after being shot in the war. Our patient was also wounded during the war and received blood transfusion.

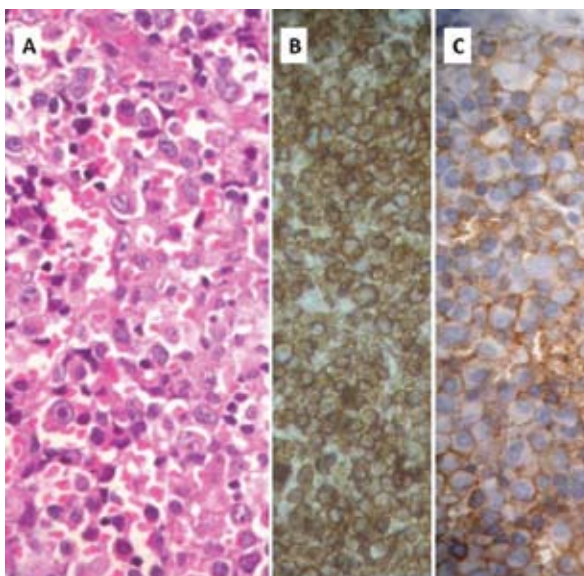
In laboratory studies, there were no abnormal hematologic and biochemical results. Except for the elevated rheumatoid factor level, which was 128 IU/mL, all of the rheumatology related serologic tests including antinuclear antibody, anti-PR3 and anti-MPO were negative and serum complements were normal. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were not elevated. Tuberculin skin test was negative. Viral serologic studies yielded negative results for HIV and hepatitis C virus antibodies but hepatitis B surface antigen (HBs) and anti-HBs



**Figure 1.** Scattered light and dark papules resembling plane warts on the arm.



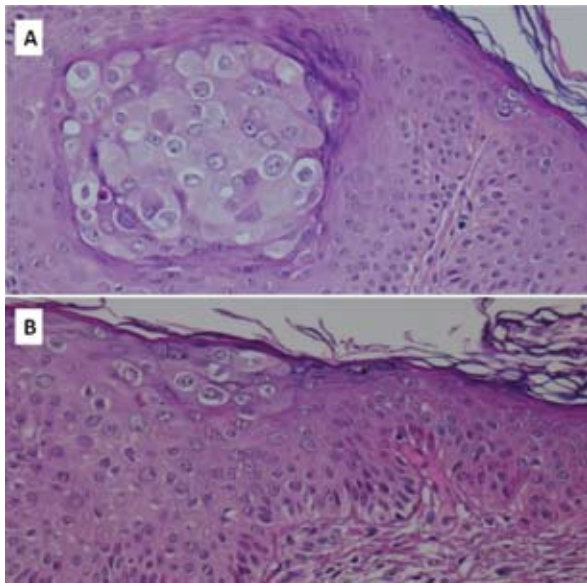
**Figure 2.** Umbilicated flesh colored 0.5×0.5 cm papules (molluscum contagiosum-like lesions).



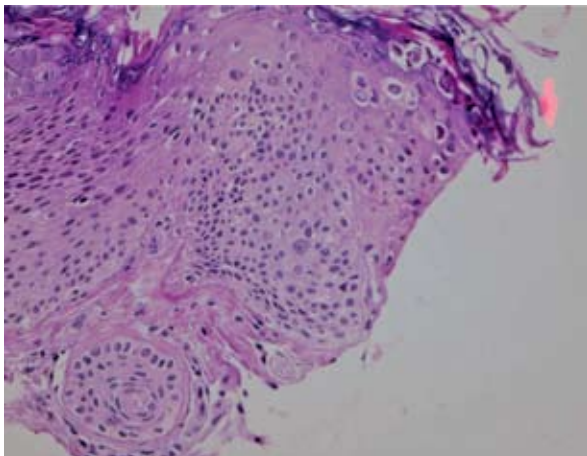
**Figure 3.** (A-C). Microscopic examination of biopsy specimen from subglottic mass showing lymphoid infiltration composed of large atypical cells (A), which were positive for LCA (B) and CD138 (C) (magnification 40X).

antibody were positive. Chest x-ray showed patchy infiltration in the upper and middle lung lobes. The patient underwent echocardiography, which showed aortic aneurysm with 4-cm median diameter.

Direct laryngoscopy revealed a polypoid subglottic mass, measuring 1.5×1×0.5 cm. Microscopic examination of biopsy specimen from subglottic mass showed an infiltrative lymphoid neoplasm composed of large atypical cells, consistent with dif-



**Figure 4.** (A, B). Nests of swollen and large cells in the granular and upper spinous layer (H&E; X400).



**Figure 5.** Dysplastic epidermal cells (H&E; X100).

fuse large-cell lymphoma with plasmablastic features (plasmablastic lymphoma), which was positive for LCA and CD138 and negative for cytokeratin, CD3, CD20, CD43 and CD30 on immunohistochemistry (Fig. 3). Bone marrow aspiration result was normal. Skin lesion biopsy revealed specific cytopathic effect seen in various HPV types associated with EV including thickened epidermis with nests of swollen and large cells in the granular and upper spinous layer, clear nucleoplasm, conspicuous perinuclear halo and cytoplasmic blue-gray pallor. Also there were dysplastic epidermal cells (Figs. 4 A, B and 5). There were associated eczematous changes including mild acanthosis,

spongiosis and superficial perivascular dermal lymphohistiocytic infiltration. DNA typing for HPV types detected HPV9 by PCR method, but the laryngeal mass was negative for HPV DNA. The patient underwent chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) regimen for his lymphoma. Complete response was achieved with nine cycles of chemotherapy. He has been lymphoma-free for 12-month follow-up. The skin lesions also slightly improved after chemotherapy.

## DISCUSSION

Epidermodysplasia verruciformis is a rare genetic dermatosis characterized by inherited susceptibility to infection with specific HPV types. Most cases of EV are caused by mutations in the *EVER1* or *EVER2* gene, both of which encode transmembrane-channel-like proteins in the endoplasmic reticulum that may act as restriction factors for defective  $\beta$ -papillomaviruses in keratinocytes (9,10). Lesions of EV are occasionally located on sun-exposed sites of the face, trunk and extremities. It usually presents with pityriasis versicolor-like lesions and reddish verrucose plaques or plane warts (1). EV-associated HPV types are 3 and 10 (both characteristic of plane wart in non-EV patients) as well as types more distinctive to EV such as 5, 8, 9, 12, 14 and 15 (11).

Immunosuppressed patients, those with hematologic malignancies, transplant recipients and HIV positive patients could develop acquired EV-like eruptions (3-5,12).

Some abnormalities of nonspecific cell-mediated immunity have been found in patients with EV. These include decreased absolute numbers of T lymphocytes and T helper cells with a reversed CD4+/CD8+ ratio (2,13).

Extracutaneous cancers reported in EV are lymphoma, astrocytoma, and intestinal adenocarcinoma (7,8,14). Our patient presented at age 27 with diffuse large cell lymphoma of plasmablastic type after a long history of EV. A similar association of EV, disseminated molluscum contagiosum and intestinal diffuse large B cell lymphoma has been published previously (5).

Increased risk of diffuse large B-cell lymphoma has been observed in association with viral infections and treatments and diseases that suppress the immune system, including autoimmune diseases, organ transplants, and primary or acquired immunodeficiencies (15,16).

The inherent defect in immunosurveillance associated with EV could predispose the patients to development of this malignancy. The concurrence of molluscum contagiosum in our patient is in favor of underlying T-cell deficiency.

The plasmablastic lymphoma that developed in our patient is a distinctive B lymphocyte neoplasm that shows diffuse proliferation of large neoplastic cells, most of which resemble immunoblasts and have immunophenotype of plasma cells (17). Plasmablastic lymphoma was originally described in patients with HIV as a subtype of diffuse large-cell lymphoma, presenting almost exclusively with jaw and oral mucosa involvement (18), however, its occurrence in a number of HIV-negative patients has been reported thereafter (19,20).

Interestingly, our patient had been incidentally affected with HBV infection. There is a report indicating concomitant presence of squamous cell carcinoma and hepatocellular carcinoma in a patient with EV and associated chronic HBV infection (21).

## CONCLUSION

It is not clear if the co-infection with HBV could support the development of secondary malignancies in EV patients. EV patients should receive regular follow-up for possible cutaneous or extracutaneous malignancy. Patients should be at least advised to reduce UV exposure and monitoring is mandatory if radiotherapy is necessary for the management of lymphoma.

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