Epidermodysplasia verruciformis associated with isolated IgM deficiency

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ABSTRACT

A 20 year-old man presented to our clinic with multiple warts on both hands and tumoral lesions on his face but otherwise healthy. On dermatological examination, numerous brown-black papular lesions, changing from 2 to 5 cm in diameter were found on his face along with multiple, flesh-coloured, flat-topped papules on the dorsa of his hands. A tumoral lesion, approximately 3 cm in diameter on the right side of his forehead and desquamated erythematous macules were also observed on the trunk. Laboratory investigations showed that serum immunoglobulin M (IgM) level was decreased. The histopathological examination of verrucous lesions on the hands was consistent with epidermodysplasia verruciformis and the histopathological diagnosis of the tumoral lesion was squamous cell carcinoma.

Key Words: Epidermodysplasia verruciformis, IgM deficiency, Immune system

Epidermodysplasia verruciformis (EV) is a rare genodermatosis caused by human papillomavirus (HPV) types 3, 5, 8-10, 12, 14, 15, 17 and 19-25.[1,2] Although most EV patients have been found to have an impaired cell-mediated immunity, their humoral immunities have so far been known to be preserved. We report only the second instance reported case of epidermodysplasia verruciformis with IgM deficiency.

CASE REPORT

A 20 year-old man presented to our clinic with multiple warts on both hands and tumoral lesions on his face. His history revealed a skin cancer on his scalp which was excised at another center three years ago. His sister had similar lesions.

On physical examination, there was no pathology except the skin lesions. On dermatological examination, numerous, brown-black papular lesions, ranging from 2 to 5 cm in diameter were found on his forehead and chin along with multiple, flesh-coloured, flat-topped papules on the dorsa of his hands [Figure 1]. A tumoral lesion, approximately 3 cm in diameter covered with hemorrhagic crusts was seen on the right side of his forehead along with desquamated erythematous macules on the trunk [Figure 2].

Laboratory findings including complete blood count, urinalysis and serum glucose level were within normal limits. Hepatitis, tumor markers and anti-human immunodeficiency virus (anti-HIV) antibodies were absent. Serum IgA, IgG, C3 and C4 levels, measured by nephelometric technique were within normal limits, whereas the serum IgM level was found to be decreased [IgM: 0.336 g/L (age-related normal values = 0.50-3.20 g/L)]. No pathologic finding was found in the chest roentgenogram, cranial tomography and abdominal ultrasonography. Multiple biopsies were taken from the tumoral lesions on the forehead, pigmented lesions on the chin and verrucous lesions on the hands.

The histopathological examination of the pigmented lesion on the chin was consistent with actinic keratosis. The histopathological examination of verrucous lesions

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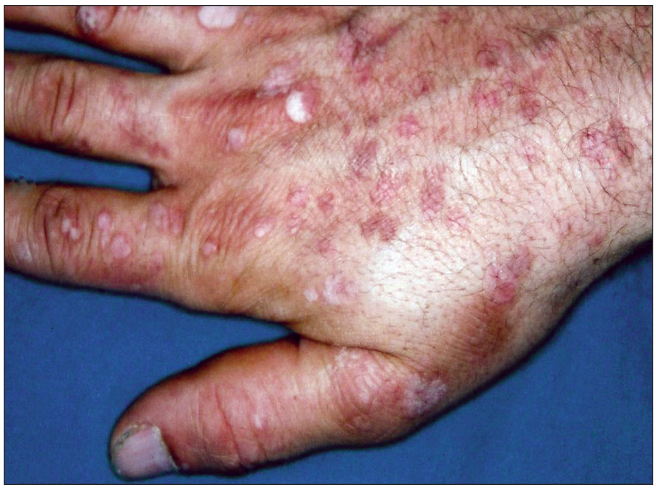

Figure 1: The flesh-colored, flat-topped papules on the dorsa of the hands

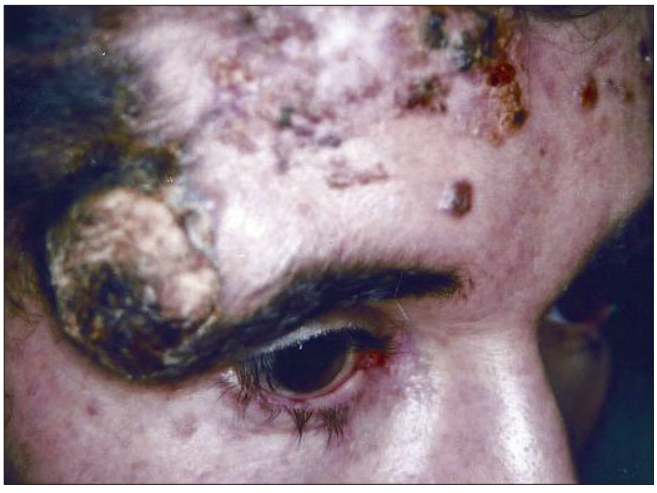

Figure 2: The actinic keratoses, verrucous lesions and tumoral lesion on the forehead

on the hands revealed irregular epidermal hyperplasia, hypergranulosis and keratinocytes including viral inclusion bodies. These findings confirmed the diagnosis of "EV". An immunohistochemical examination revealed keratinocyte nuclei stained brown with polyclonal HPV antibodies. The tumoral lesion was histopathologically diagnosed as squamous cell carcinoma (SCC). The case was appraised as an autosomal recessive trait on genetic consultation. The tumoral lesion was totally excised and the patient is still being followed up.

DISCUSSION

Epidermodysplasia verruciformis is a rare genodermatosis characterized by disseminated infection by HPV.[1,3] The lesions of EV usually begin in childhood and continue throughout the patient's lifetime. Skin lesions on the dorsal surfaces of the hands, extremities and face include flat, wart-like papular lesions, which are usually caused by the same HPV types found in flat warts in the general population. On the trunk, there are red-brown, slightly scaly macules resembling tinea versicolour that are caused by EV-HPV types.[1,3,4]

About 50% of all EV cases are inherited, usually with an autosomal recessive pattern. X-linked inheritance has also been reported.[1,3,5] The sister of our patient had similar lesions on this skin. The case was appraised as autosomal recessive trait after a genetic consultation.

The pathogenesis of EV may be explained by three different factors: genetic factors, immunological factors and HPV infection. Although most EV patients have been found to have an impaired cell-mediated immunity, it is still not known whether the impairment of the immune response is primary or secondary to massive HPV infection.[6] There are subtle changes in lymphocyte function such as lymphopenia with a reduced B cell/T cell ratio but a normal T helper/T suppressor ratio in some patients. Sometimes, reduced spontaneous migration and chemotaxis of neutrophils can be observed. Despite these findings, the patients are not usually susceptible to other viral and bacterial infections.[7] Majewski *et al*. reported that natural cell-mediated cytotoxicity was in the normal range in EV patients.[8] It has been thought that the basic immunological defect might be the inability to recognize EV-specific HPVs in EV patients.[6]

There are also case reports regarding the association of idiopathic CD4 lymphocytopenia with epidermodysplasia verruciformis-like eruptions.[9,10] Idiopathic CD4 lymphocytopenia possibly caused by an as-yet unidentified virus or viruses varies from minimal abnormalities to fatal opportunistic infections. In these cases, the absence of evidence of HIV-1 infection should be noted.[11] Our patient did not have any findings of opportunistic infections. Therefore, the CD4 lymphocyte count was not examined.

Epidermodysplasia verruciformis patients are not prone to bacterial, fungal or viral infections with the exceptions of HPVs associated with plane warts.[1] Their humoral immunities are known to be preserved. However, Iraji and Faghihi reported a case of EV associated with decreased serum IgM levels. The serum IgM level of their patient was as low as 60 mg/dL (normal range: 73–267 mg/dL). In selective IgM deficiency, eczema and persistent, large, viral warts may be present but the main clinical problems usually consist of meningecoccal and pneumococcal infections. Their case had no other pathology except EV.[7] Similarly, our case had EDV associated with selective IgM deficiency but was otherwise healty.

Multiple skin cancers such as Bowen's disease, squamous cell carcimonas (SCC), actinic keratoses, basal cell carcinomas and sweat apparatus carcinomas develop in one-third of EV patients in sun-exposed areas.[6] Although it is still unclear which EV-HPVs are responsible for the development of malignant lesions, HPV-5 and -8 are considered the biggest culprits.[1,2,8] Our case developed SCC.

This case is the second reported case of EV associated with IgM deficiency although this finding may be just coincidental. However, the case of EV with an isolated IgM deficiency previously reported by Iraji and Faghihi and our case raise the question as to whether selective IgM deficiency can play a role in the pathogenesis of EV or whether there can be a genetic association between these disorders. Studies with a large number of EV patients can clarify whether there is an actual relationship between EV and IgM deficiency.

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