Epstein-Barr Virus-associated Oral Papulosis in Graft-versus-host Disease

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We report here a case of a patient who had received allogeneic haematopoietic stem cell transplantation for secondary acute myeloid leukaemia, and developed, on top of a lichenoid mucosal chronic graft-versus-host disease (GvHD), an Epstein-Barr virus (EBV)-associated papular eruption. This disorder, for which we propose the term EBV-associated oral papulosis (EAOP), probably occurred as a consequence of long-term immunosuppressive therapy and may represent an as yet unrecognized sign of immunodeficiency.

CASE REPORT

Five months after haematopoietic stem cell transplantation, when still immunosuppressed with prednisolone and cyclosporin A for chronic GvHD of the skin and mucous membranes, a 47-year-old female patient presented with painful broad-based whitish papules on the edges and top surface of the tongue (Fig. 1A). These lesions had developed several days previously, and were occasionally surrounded by erosions and superficial ulcers covered by debris (Fig. 1A) and, in the absence of any topical medication, were slowly progressive. The patient was immunologically reconstituted, with white blood cell counts and immunoglobulin levels within the normal range, and exhibited signs of chronic cutaneous GvHD, including a lichenoid rash of the face and the extremities as well as xerosis of skin, xerostomia and xerophthalmia. Differential diagnoses of the oral lesions included chronic GvHD, secondary syphilis, hypertrophic oral candidiasis, verrucous herpes-simplex virus (HSV) infection, and human papillomavirus (HPV)-associated acanthomas. The last four diagnoses could be excluded by a negative syphilis serology, by negative results of fungal cultures and by the failure to amplify HSV as well as HPV nucleic acid sequences from swabs of the tongue. Because of prolonged immunosuppression, and despite the rather atypical presentation, we also considered oral hairy leukoplakia (OHL) as a possibility and, thus, tested for EBV by PCR from a lesional swab. This procedure yielded a positive result (Fig. 2), as did an EBV-, but not a HSV and cytomegalovirus (CMV) *in situ* hybridization from a biopsy specimen. Histopathological analysis of lesional mucosa revealed an irregular parakeratosis, acanthosis, focal balloon cells and pale staining of keratinocytes as unspecific viral-induced morphological changes, as well as epithelial giant cell formation, a feature of HSV or varicella-zoster virus infection, but not of OHL (Fig. 3). The dense lichenoid dermal infiltrate histologically confirmed the diagnosis of chronic GvHD of the mucous membranes.

Fig. 2. Polymerase chain reaction testing of a swab of the tongue for Epstein-Barr virus (EBV) revealed clearly positive results (*lane 4*). The EBV-positive Raji cell line was used as positive control (*lane 1*). Water (*lane 2*) and an irrelevant DNA (*lane 3*) served as negative controls.

Systemic prednisolone therapy was continued, although at a reduced dosage, as the patient had severe GvHD that required systemic immunosuppression, and topical treatment of the skin and mucous membranes with tacrolimus ointment and steroid creams, respectively, was intensified. At the same time the patient received valacyclovir 1 g three times a day as this treatment is known to be: (*i*) safe even in higher dosages (1); (*ii*) adequate as long-term therapy; and (*iii*) effective in HIV-infected patients with OHL (2). The patient noticed a prompt reduction in symptoms and the tongue appeared to be greatly improved within 2 weeks (Fig. 1B). After a 4-week course of treatment with valacyclovir the patient was free of symptoms and there was no evidence of a relapse of the papules on the tongue during a follow-up period of 12 months.

DISCUSSION

Taken together, the patient had a mucosal disorder caused by a herpes virus with a rapid and profound therapeutic response to oral valacyclovir. Although giant cell formation in histology favours HSV or CMV infection, we did not detect either type of herpes vi-

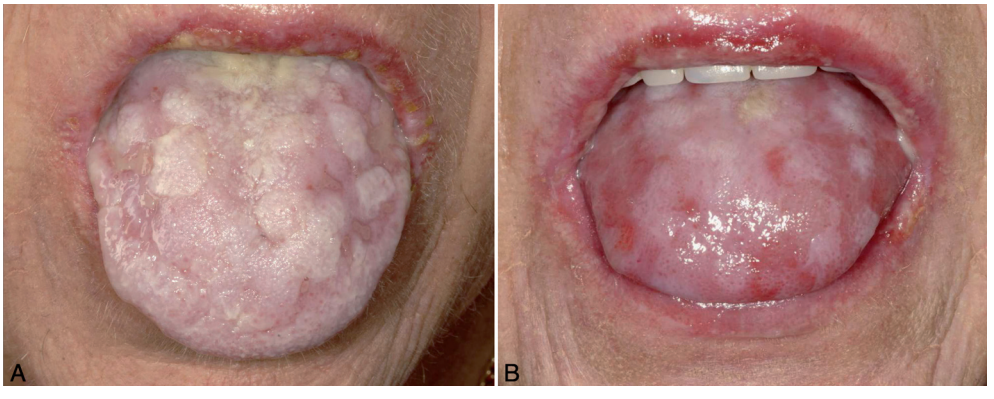

Fig. 1. (A) Painful broad-based whitish papules at the edges and surface of the tongue with small erosive patches in between. (B) Improvement of the symptoms and clinical appearance of the tongue after 2 weeks of valacyclovir therapy.

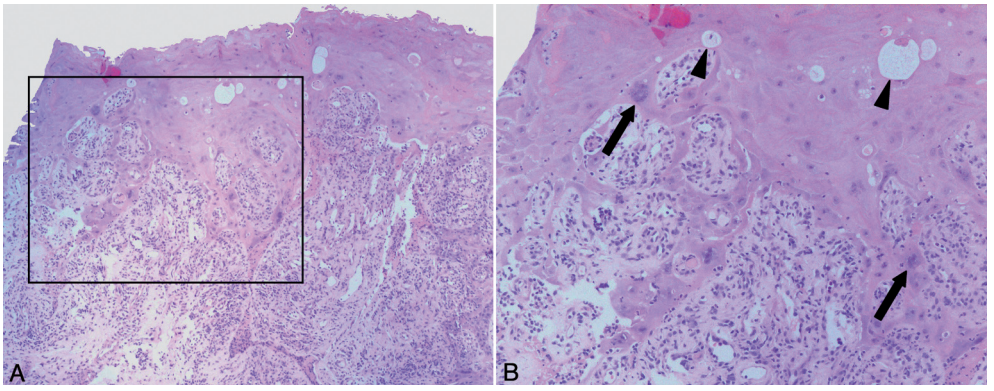

Fig. 3. Histopathology of a tongue specimen showed a dense lichenoid dermal infiltrate and epidermal alterations including acanthosis and focal balloon cell changes of keratinocytes (*arrowheads*) and epithelial giant cell formation (*arrows*). B is a higher magnification of A.

ruses by PCR or by *in situ* hybridization. In contrast, the presence of EBV could be demonstrated by both methods. The characteristic EBV-associated mucosal disease in immunosuppressed individuals is OHL. This usually presents as linear lesions restricted to the edges of the tongue without epithelial giant cell formation (3), features distinctive to those described here. We therefore considered the possibility that the patient may have had an as yet unrecognized form of an EBV-associated mucosal disorder, EAOP.

The rationale for our therapeutic approaches with reduced systemic immunosuppression and anti-viral therapy was based on the reported treatment success of HIV-infected patients with OHL after reversal of immunosuppression (e.g. by combination antiretroviral therapy in HIV-infected patients (3)) as well as with certain antiviral drugs (2, 4–6).

Different forms of oral EBV-associated diseases have been described. Since the immune system is critical in preventing the progression of EBV disease, the immunological status of the patient plays a crucial role in the subsequent development of pathologies, and immunocompromised patients are therefore more likely candidates for developing EBV-associated diseases (7). Primary EBV-infection can either result in an asymptomatic course or cause mucocutaneous manifestations in infectious mononucleosis or other acute EBV-associated syndromes (8). Latent EBV infections may lead to OHL, lymphoproliferative disorders such as plasmablastic lymphoma, particularly in immunocompromised patients (9), or malignant conditions such as Burkitt's lymphoma and nasopharyngeal carcinoma. OHL occurs almost exclusively in HIV-infected patients and is a marker of advanced immunosuppression (10). In patients who are immunosuppressed for reasons other than HIV, OHL is an uncommon disease; however, clinical symptoms do not differ between HIV^+ and HIV^- patients (11, 12). Further studies are needed to determine whether the clinical and histopathological findings of EAOP are characteristic for specific forms of immunosuppression and, ultimately, whether EAOP represents a new disease or an atypical papular variant of OHL.

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