Extranodal NK/T-cell Lymphoma, Nasal Type, Possibly Arising from Chronic Epstein-Barr Virus Infection

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Sir,

Extranodal natural killer (NK)/T-cell lymphoma, nasal type, which is most prevalent in Asia, Mexico, and Central and South America (1), shows a strong association with Epstein-Barr virus (EBV) infection, particularly in Asian patients (2). Patients with nasal involvement show symptoms of nasal obstruction or epistaxis due to the presence of a mass lesion. However, the lesion may disseminate rapidly to various sites, e.g. the skin, gastrointestinal tract, or cervical lymph nodes, during the clinical course. The skin is commonly involved in the formation of nodules, often with ulceration (3–5). We describe here a patient who was finally diagnosed with extranodal NK/T-cell lymphoma, nasal type, possibly arising from chronic indolent EBV infection with skin eruptions as an initial symptom. There are no other reports except for hydroa vacciniforme and hypersensitivity to mosquito bites (6) in the literature of chronic inflammatory infiltrates associated with EBV shown to precede the development of NK/T-cell lymphoma. This is the first case, which can be determined retrospectively, to show the existence of EBV in a skin sample.

CASE REPORT

A 60-year-old woman was referred to our hospital with a 2-year history of recurrent swelling of the upper lip, the skin adjacent to it, and cheeks, without systemic symptoms (Fig. 1a). Laboratory examinations, including a peripheral blood cell count and liver and renal function tests, were within normal limits. Histological findings of the skin above the upper lip showed oedema with lymphocyte infiltration in the upper to middle dermis (Fig. 2). An initial diagnosis of granulomatous cheilitis and pareiitis (inflammation and swelling in the cheeks) was made at that time from the clinical and histological findings. The oral administration of prednisolone, 10–20 mg/day, reduced the swelling of the lip and skin. However, the patient decided to discontinue medication after several months, resulting in repeated exacerbation of the lesion on the upper lip and cheeks.

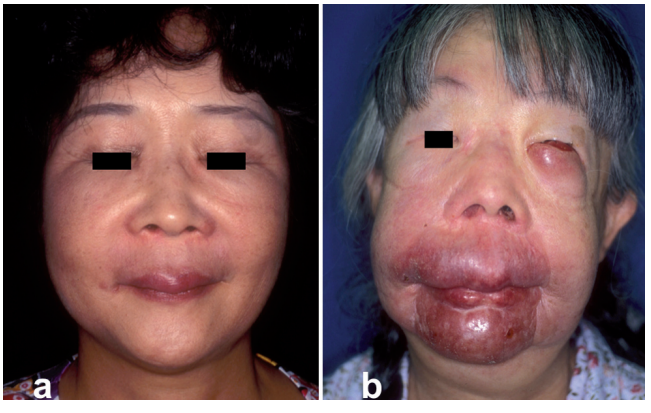

Fig. 1. Clinical findings. (a) Swelling of the upper lip, skin adjacent to it, and cheeks was observed at the first consultation. (b) Induration and tumours with erythema on the lower and upper chin and bilateral cheeks were observed 9.5 years later. The relatives has approved the publication of these photos.

She visited our hospital again 9.5 years later because of induration and erythematous tumours on the lower and upper chin, bilateral cheeks, right upper arm, and bilateral axillae (Fig. 1b). These lesions had rapidly increased 2–3 months prior to this consultation. As we clinically considered this case to be malignant lymphoma, we performed a biopsy of the tumour. Histological findings from the cheek showed atypical lymphocyte infiltration throughout the entire dermis (Fig. 2). The profile of the infiltrated lymphocytes was cytoplasmic $CD3^+$ (polyclonal antibody), $CD4^-$, $CD8^-$, $CD20^-$, $CD43^+$, $CD45RO^+$, $CD56^+$, and $CD79a^-$, with positive staining for EBV early region protein (EBER)-1 (Fig. 2). The serum soluble IL-2 receptor level was high (2113 U/ml), and antibodies to EBV viral capsid antigen (VCA) IgG, IgA, and early antigen (EA) IgG were 10, 240, 640, and 2560, respectively. In addition, EBV DNA was detected at 1×10^5 copies/ml in peripheral blood by real-time polymerase chain reaction (PCR). A computed tomography scan showed a tumour in the nasal cavity and swelling of the bilateral inguinal, axillary, and cervical lymph nodes. A final diagnosis of extranodal NK/T-cell lymphoma, nasal type, was made and five courses of DeVIC therapy (etoposide (VP-16), ifosfamide (IFM), dexamethasone, and carboplatin (CBDCA)) (4) were given. Although a partial response was achieved, the patient died of lymphoma 8 months after the chemotherapy.

A retrospective examination of the histology of the skin biopsy from the first consultation showed that the phenotype of lymphocytes was mainly $CD20^-$, $CD45RO^+$, and $CD56^-$, and a proportion of the lymphocytes expressed CD8 or CD4. In addition, the lymphocytes infiltrating in the dermis on the first consultation were also positive for EBER-1 (Fig. 2). These findings raised the possibility that extranodal NK/T-cell lymphoma, nasal type, could appear after a prolonged period of indolent EBV infection.

DISCUSSION

The most typical immunophenotype of extranodal NK/T-cell lymphoma is: $CD2^+$, $CD56^+$, surface $CD3^-$, and cytoplasmic $CD3\varepsilon^+$. Other T- and NK-cell-associated antigens are usually negative, including CD4, CD8, CD43, and CD45RO (1). Many investigators include lymphomas that demonstrate the $CD3\varepsilon^+$, $CD56^-$, cytotoxic $molecule^+$, EBV^+ phenotype among the nasal-type NK/T-cell lymphomas, since these cases show a similar clinical disease as cases with CD56-positive expression (1). The phenotypes of infiltrating lymphocytes in the

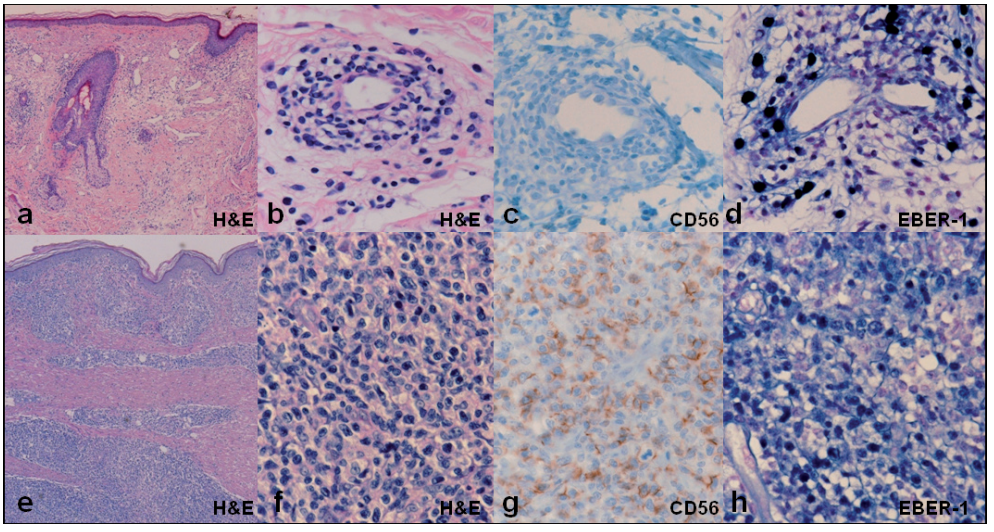

Fig. 2. Histological findings of the skin above the upper lip on (a–d) the first consultation and (e–h) the tumour 9.5 years later. Detail of the images, from left to right: haematoxylin and eosin (H&E) staining at low and high magnification, CD56 stain (c is negative, g is positive (*brown*)), and Epstein-Barr virus early region protein (EBER)-1 stain (both d and h are positive (*deep blue*)).

present case were distinct between two different points in time; $CD56^-$ on the first consultation and $CD56^+$ 9.5 years later. There are three possible explanations for this inconsistency: (*i*) the phenotype of infiltrating lymphocytes changed during the long clinical course; (*ii*) initially, oligoclonal lymphocyte clones proliferated, including both $CD56^+$ and $CD56^-$ clones, but the $CD56^-$ clone was dominant and, after a prolonged period, the $CD56^+$ clone survived with selective proliferation among the clones; and (*iii*) initially, $CD56^-$ clone, possibly $CD8^+$ cells infiltrated and afterwards, independently $CD56^+$ clone was proliferated.

Extranodal NK/T-cell lymphoma, nasal type, occurring outside the nasal cavity is highly aggressive, leading to short survival times and a poor response to therapy (3–5). The expression of multi-drug resistance genes may contribute to chemotherapy resistance in a majority of cases. The prognosis of this disease is variable, with some patients responding well to therapy and others dying of disseminated disease despite aggressive therapy (7). A partial response was transiently obtained in the early stage by DeVIC therapy in our patient, but unfortunately she died of lymphoma after 8 months.

We describe here a patient initially diagnosed with granulomatous cheilitis and pareiitis, and finally diagnosed with extranodal NK/T-cell lymphoma, nasal type, after 9.5 years. Histologically, lymphocytes infiltrating in the dermis showed positive staining for EBER-1 not only 9.5 years later, but also on the first consultation. Although this case did not fulfil the criteria of chronic active EBV infection (8, 9), there is a possibility of extranodal NK/T cell lymphoma, nasal type, appearing after a prolonged period of indolent EBV infection. The skin lesions of extranodal NK/T-cell lymphoma, nasal type, commonly appear around the nasal cavity. Thus, this disease should be considered among the differential diagnosis of skin diseases around the nose.

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