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Case Report

Epstein-Barr virus-associated smooth muscle tumor in patients with acquired immunodeficiency syndrome

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Epstein-Barr virus (EBV)-associated smooth muscle tumor (SMT) is a recognized but uncommon disease that is found to occur in patients with immunocompromised conditions such as acquired immunodeficiency syndrome (AIDS). These tumors may be multifocal and located at unusual sites, such as the brain and liver. This report describes the case of 2 AIDS patients with EBV-associated SMT and highlights the features and outcome of this rare but potentially important tumor in human immunodeficiency virus management.

Key words: Acquired immunodeficiency syndrome; Epstein-Barr virus infections; In situ hybridization; Smooth muscle tumor

Introduction

Epstein-Barr virus (EBV) is a well-known pathogen that is responsible for a variety of diseases in people with impaired immune function, notably, defective cell-mediated immunity. In human immunodeficiency virus (HIV)-infected patients, EBV is universally associated with acquired immunodeficiency syndrome (AIDS)-related central nervous system lymphoma [1]. EBV-associated smooth muscle tumor (SMT) is a recently recognized neoplasm in patients with immunosuppression [2-4]. We report the case of 2 AIDS patients with EBV-associated SMT at our HIV clinic in Hong Kong from 2002 to 2004.

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Case Report

Case 1

Patient 1 is a 43-year-old Chinese man, who was diagnosed as HIV-positive in December 2001, having presented with *Pneumocystis jerovecii* pneumonia and disseminated *Mycobacterium avium intracellulare* (MAI) infection. His nadir CD4 count was 51 cells/μL. Following treatment of the opportunistic infections, he was administered combivir/3TC/ritonavir-boosted indinavir. He responded well with full viral suppression and gradual increase in CD4 levels. In May 2002, he was first noticed to have 2 non-painful fleshy nodular masses over the lateral tongue and vocal cord. Excision biopsy done for progressive increase in the number of lesions revealed an SMT/perivascular myoid cell tumor. The lesions showed strong nuclear positivity for EBV mRNA (EBER) by in situ hybridization.

Nine months later, the patient presented with slowly progressive left eye ptosis and diplopia. Examination revealed 3rd, 4th, and 6th cranial nerve palsies. His CD4

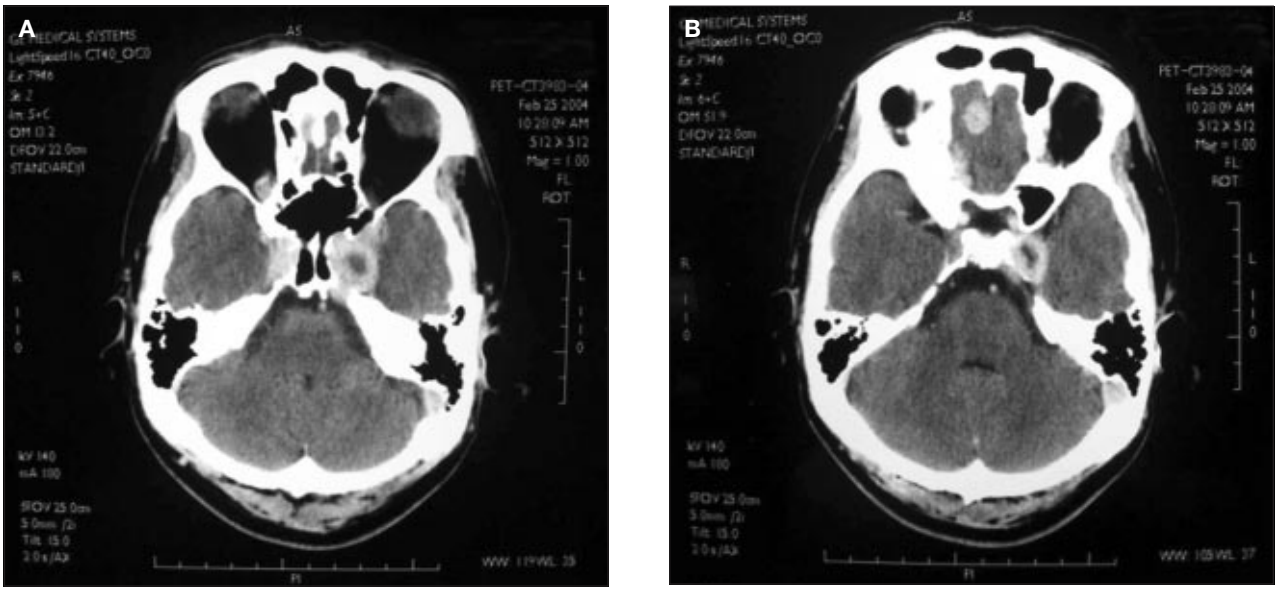

Fig. 1. Computed tomography scan of Patient 1 showing contrast-enhanced extra-axial brain lesions in both parasellar regions, right anterior cranial fossa, and right orbital apex without surrounding edema.

count was 200 cells/μL. Magnetic resonance imaging and computed tomography scans of the brain showed multiple enhancing extra-axial lesions in the right frontal lobe, parasellar regions, right anterior cranial fossa, and right orbital apex, each measuring 1 to 2 cm in diameter without surrounding edema (Fig. 1). Plasma was found to be positive for EBV by polymerase chain reaction. Serum EBV viral capsid antigen polyvalent antibody and immunoglobulin A antibody titers were 1:5120 and 1:80, respectively. Craniotomy with open excisional biopsy of the frontal lesion revealed a solid fibrotic tumor with a well-defined capsule. Histological examination (Fig. 2A and Fig. 2B) showed EBER-positive SMT/myoid cell tumor, as observed in the case of the oral lesions. A 10-day course of palliative focal radiotherapy was given over 2 weeks. The patient improved clinically with partial recovery of the cranial nerve palsies and resolution of ptosis and diplopia, more than 12 months post-surgery. There was no recurrence of the oral tumors. After diagnosis of SMT, he was maintained on a highly-active antiretroviral therapy (HAART). CD4 count was about 300 cells/μL, with full virologic suppression.

Case 2

Patient 2 is a 37-year-old Thai female who was diagnosed as HIV-positive in 1994 but had not received HIV care. In August 2004, she presented with 6 months of persistent fever and weight loss that was found to be due to disseminated MAI. Incidentally, during work-up of deranged liver function with respect to raised alkaline phosphatase level (173 U/L), ultrasonogram showed a 5 cm × 4 cm × 5-cm heterogeneous mass at the inferior edge of the right lobe of the liver. Follow-up abdominal computed tomography showed a contrast-enhanced round mass with a hypodense center in segment 6, with splenomegaly but no ascites or para-aortic lymph node enlargement. Amoeba serology was negative and she was empirically treated for pyogenic liver abscess. The mass persisted and a fine needle aspiration biopsy was done which showed spindle cell tumor with positive staining for actin, suggestive of smooth muscle differentiation. Serum EBV capsid antigen polyvalent and immunoglobulin A antibody titers were 1:1280 and <1:10, respectively. She was put on observation for the liver tumor. Kaletra™ (Abbott Laboratories, Abbott Park, IL, USA)-based HAART was started. MAI was controlled with azithromycin, ethambutol, and levofloxacin. Nine months later, her CD4 count increased from a nadir of 2 cells/μL to 195 cells/μL, while her plasma HIV-1 viral load remained <400 copies/mL. A follow-up ultrasonogram, 11 months after the diagnosis of SMT, showed that the size of the liver mass had remained unchanged.

Discussion

Immunosuppression leading to the emergence of SMT was first described over 30 years ago [5]. However, this link between immunosuppression and SMT occurrence

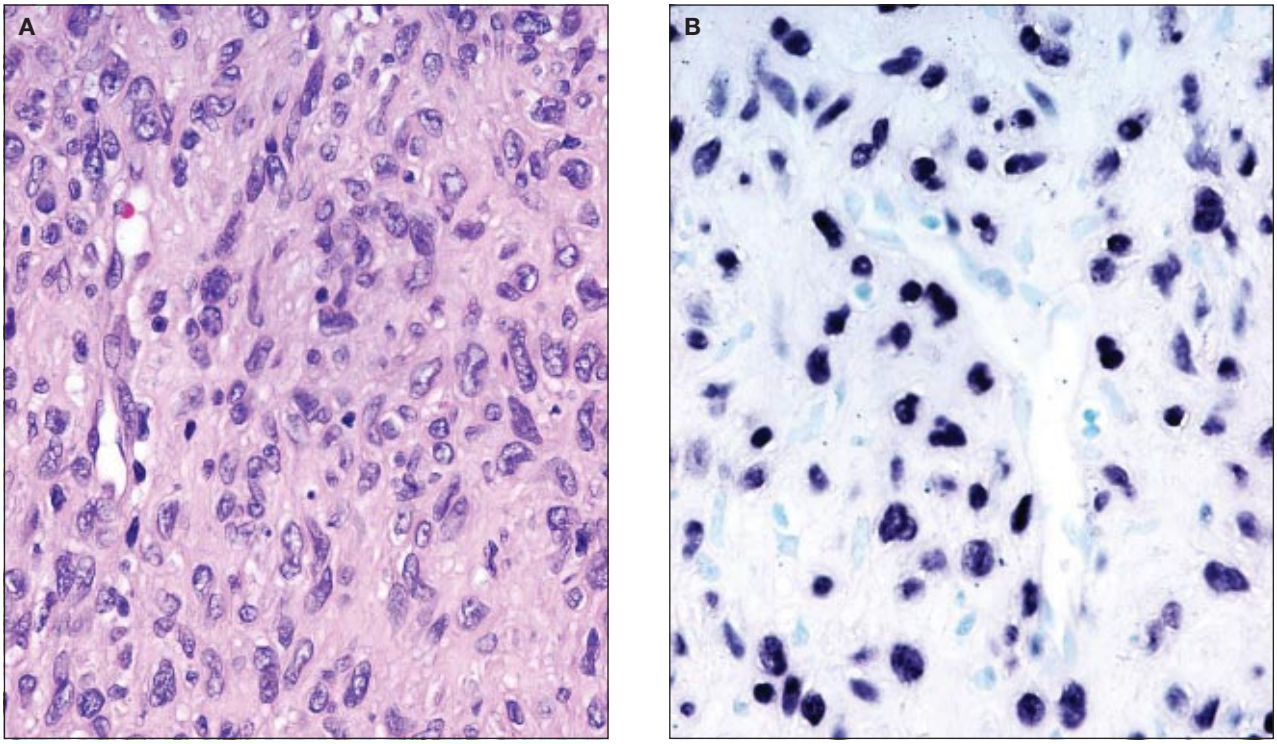

Fig. 2. (A) The plump spindle-shaped cells with fusiform eosinophilic cytoplasm arranged mainly in short fascicles between the fibrous stoma. Mild nuclear pleomorphism and hyperchromasia are noted (hematoxylin and eosin stain, original magnification x 400). (B) In situ hybridization (ISH) for Epstein-Barr virus (EBV) mRNA (EBER). Prominent nuclear positivity for EBER is evident and indicates the presence of latent EBV infection (ISH for EBER, original magnification x 400).

became prominent only in the last decade, given the increased number of AIDS patients and transplant recipients. Although the linkage was definitively proven in 1995, EBV-associated SMT in immunocompromised subjects [6,7] is still an uncommon mesenchymal tumor. To date, the largest series (9 AIDS patients) was reported in Thailand [8]. The 2 SMT cases described here account for a prevalence of 0.5% among all our new patients seen during the 3-year period. On the other hand, the cumulative prevalence of SMT occurrence has been 0.15% at our clinic for HIV-infected adults since 1987. There is a possibility of underestimation of the condition due to incorrect diagnosis. A noteworthy point is that this condition was not detected in Caucasian patients — another significant ethnic group in our HIV clinic. Presumably, all the 9 patients in the Thai study [8] were Thai or Asians. However, the possibility of an ethnic variation in the frequency of the tumor requires further studies.

Children and adolescents are actually the population of predilection among reports of EBV-associated SMT, mostly complicating HIV infection [9,10] and post-transplantation [7,11], followed by congenital immunodeficiency syndromes [12]. The tumor was found to spread throughout the body from solid organ through the internal viscera, including the liver [13,14], spleen [14,15], thyroid [16], brain [12,14,17], gastrointestinal tract [6,9], and lungs [9,14]. Clinical manifestations of EBV-associated SMT are also diverse in adults, with possible involvement of different sites such as the liver, heart, lung, spinal cord, and brain [2,8,18-20]. The tumor is characterized by its potential to be multicentric or multifocal [8,9,14,18,19]. Treatment with surgical resection and reduction of immunosuppressive agents has been reported with some success in post-transplant patients [7,13,21]. It is not clear whether immune recovery after HAART serves to control the SMT in HIV-infected patients.

The features exhibited by the 2 patients reported here have similarities as well as differences when compared to other case reports. Despite a modest CD4 count in response to HAART, Patient 1 still developed progressive SMT; this is in contrast to the universal low immune level in the Thai series [8]. The locations of the intracranial tumors were, however, consistent with other reports of dural-based or intracranial EBV-associated SMT in HIV-infected patients [4,22]. The laryngeal SMT observed in this case has rarely been reported [23].

Similarly, primary hepatic SMT in adult AIDS patients, as occurring in Patient 2, was seldom reported [8]. It is possible that there are other sites of involvement, and that we have not carried out a complete investigation or the underlying lesions take time to manifest overtly. The presence of EBV is similar to that in previous reports [2,6,7,24]. It can be difficult to distinguish histologically between distant metastases and multicentric presentations for EBV-associated SMT [25]. The clinical status of Patient 1 improved upon tumor resection and HAART continuation and that of Patient 2 was stable upon observation and HAART initiation, indicating that the short-term prognosis of SMT in AIDS patients can be good. In summary, EBV-associated SMT is an uncommon but important tumor in HIV management. The tumor should be borne in mind in the setting of space-occupying lesions of organs in AIDS patients, especially when there are multiple and unusual sites of involvement.

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