Case Report

Epstein-Barr Virus Associated Primary Intracranial Smooth Muscle Tumor in HIV Positive Patient: Case Report and Review of the Literature

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The authors report a case of HIV-positive patient with primary intracranial smooth muscle tumor. Evidence of Epstein-Barr Virus (EBV) infection in this tumor is proven by in situ hybridization for EBV-encoded RNA (EBER). Review of the literature shows that the occurring of smooth muscle tumor at intracranial site is extremely rare and most cases are HIV-infected patient. It also shows an association with EBV infection.

Keywords: Smooth muscle tumor, Intracranial, Epstein-Barr Virus (EBV), HIV

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Primary intracranial smooth muscle tumors are extremely rare. The case reports in the English language from around the world are less than twenty cases[1]. Most cases are HIV-infected patients and included children. This tumor is also seen in organ transplant immunosuppressed patients. Review of the literature strongly shows an association between Epstein-Barr virus (EBV) and these tumors in HIV positive patients or in transplant recipients[2-11]. These tumors in HIV positive patients or in organ transplant immunosuppressed patients are identified in the other organs that are uncommon in immunocompetent patients and also show EBV association.

Case Report

A 40-year-old Thai male presented with a 2-month history of progressive right-sided headache. The analgesic drugs did not relieve the symptom, so magnetic resonance imaging (MRI) of the brain was done. It revealed a lytic expansile lesion at right Meckel's cave, right sided clivus, and right occipital condyle, size 3.4x3.1x2.4 cm. Differential diagnoses were schwannoma or chondrosarcoma. He was planned for biopsy of this tumor. Pre-operative screening test was performed and found that he was positive for anti-HIV test. However, biopsy of the tumor by transphenoidal approach was done and the initial pathological study showed spindle cell tumor. Opened craniotomy with tumor removal was planned to be performed, but the patient was lost for follow-up. Three months later, he came to the hospital again with symptoms of hoarseness of voice, dysphagia, and weight loss in addition to severe right-sided headache. MRI of the brain was done again and revealed progression of right parasellar mass with the size of 5.1x4.1x3.9 cm. The HIV infected status was evaluated again and showed that CD4 count was 5 cells/uL. Serum toxoplasma IgG antibody, Cryptococcus antigen, VDRL, and hepatitis B antigen were all negative. Anti-retroviral therapy was started. Because the enlarged tumor was inoperable, the doctor discussed with the patient about the role of radiotherapy. He accepted and then was referred to Cancer Hospital and received radiotherapy.

The brain biopsy specimen was reviewed. The low-power view reveals fragments of the tumor, showing fascicles of spindle shaped cells (Fig. 1). At high-power view, they showed elongated blunt-ended nuclei without atypia (Fig. 2). No mitosis was identified. No area of necrosis was seen. The immunohistochemical study revealed that the tumor cells diffusely expressed smooth muscle actin (SMA) (Fig. 3) and focally expressed desmin. Epithelial membrane antigen (EMA) and S-100 protein were non-reactive. Therefore, the tumor was compatible with smooth muscle tumor.

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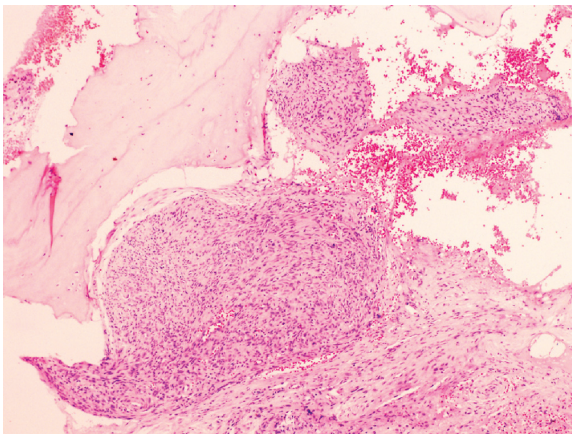

Fig. 1 Low-power view of brain biopsy shows fascicles of spindle cells (H&E, x100).

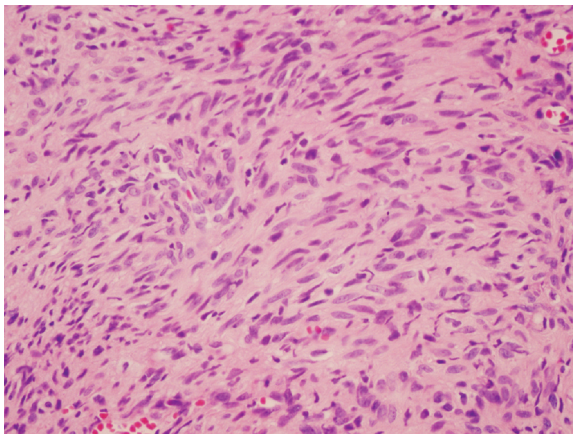

Fig. 2 High-power view shows spindle cells with elongated blunt-ended nuclei (H&E, x400).

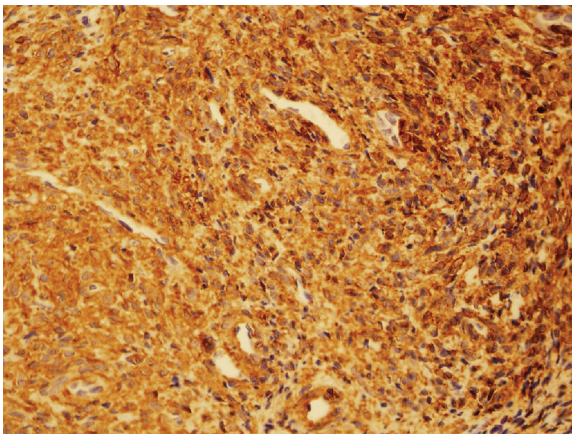

Fig. 3 Immunohistochemical study of smooth muscle actin (SMT) shows positive result (dark staining of cytoplasm) (H&E, x200).

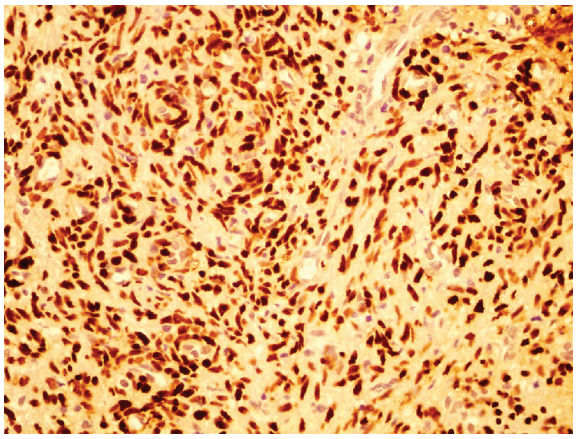

Fig. 4 In hybridization for EBV-encoded RNA (EBER) shows positive result (dark staining of nuclei) (H&E, x200).

In situ hybridization for EBV-encoded RNA (EBER) was investigated from the paraffin embedded tissue. It revealed diffuse positive (brown) staining in tumor nuclei (Fig. 4).

The radiotherapy was planned to start after receiving anti-retroviral therapy for at least 1 month. After that, he lost follow-up from the Cancer Hospital.

Discussion

Smooth muscle tumors commonly occur at uterus, soft tissue, and gastrointestinal tract. Unusual sites that have been reported in the literatures, including intracranial location, were seen mainly in HIV-infected patients or in organ transplant patients. In these cases, most of the tumors were associated with EBV infections that were approved by in situ hybridization for EBV-encoded RNA (EBER).

Review of the articles that reported about smooth muscle tumor in HIV positive patients or in organ transplant patients is summarized.

1. Epidemiology: There are published reports of these tumors from many countries, including from Thailand, the author's country[2]. This seems that there is no predisposition related to a particular ethnic group. Moreover, the tumors are reported in various age groups and in both sexes without strike predilection[2]. In another view point, smooth muscle tumor is the second most common tumor in children with AIDS[12].

2. Clinical features

- The time from HIV diagnosis to smooth muscle tumor presentation ranged from 0 month to 216 months[4].

- Location: The central nervous system (brain and spinal cord) is the common site. The

tumor may occur at dural, epidural, or extradural locations. Others common sites are the soft tissue and gastrointestinal tract that the tumors can involve from the tongue, to tonsil, stomach, small intestine, and colon[2,4]. From review of many reports, there seem to be that any location in the body can be involved by this tumor. Example of locations are; cutaneous tissue of skin[13], lung[5,14,15], pleura[4], adrenal gland[5,16], spleen[17], orbit[5,18], kidney[19], urinary bladder[4], liver[4,5,20,21], gallbladder[4], nasopharynx[4], vocal cord[4,5], bone (vertebrae, fibula)[2,4], and abdominal wall[4,5]. Some reports show multiple locations of the tumors in one organ as well as multiple tumors in multiple organs, such as pericardium and lymph node[22].

- Immune status: Smooth muscle tumors in unusual sites mainly occur in HIV-infected patients[1-34] or in organ transplant patients who receive immunosuppressant therapy[6,35,36]. There is a report of EBV-associated smooth muscle tumor that occurred at larynx in a patient with ataxia-telangiectasia[23], which is a genetic disease that also has immunosuppressive condition. Another report found smooth muscle tumor at the liver in a psoriasis patient who received immunosuppressant therapy[37]. Therefore, smooth muscle tumors in usual sites appear to arise when patients have immunosuppression from any causes. In HIV-infected patients who have this tumor, most have CD4 level less than 200 cells/uL[2]. In this reported patient, the CD4 level was only 5 cells/uL.

3. Pathology findings: The pathological diagnosis varied from leiomyoma, leiomyosarcoma, smooth muscle tumor of undetermined malignant potential, and smooth muscle tumor that was not further characterized. Patients rarely presented with both benign and malignant smooth muscle tumor[23]. It is unclear what criteria or guideline for diagnosis malignancy of smooth muscle neoplasm that the report papers used. This is because the criteria for diagnosis malignancy of smooth muscle neoplasm is not the same as in gynecologic system. However, definitive criteria for determining malignancy of smooth muscle neoplasm arising outside the gynecologic, genitourinary and gastrointestinal tracts have yet to be firmly established[2].

Gross and histology: The size of tumor ranged from 0.5 cm to 14 cm[2]. Histology of these tumors showed interlacing fascicles of spindle cells with blunt-ended nuclei and ample eosinophilic cytoplasm. Necrosis, mitosis, and cytologic atypia are noted variably from cases to cases. Some cases described an increase in cellularity and a second population of small round cells with irregular nuclear contours in addition to spindle cell population[4].

Immunohistochemical study: A wide array of immunohistochemical studies were performed in the reported literatures.

All showed positive result for smooth muscle actin (SMA)[2]. Most showed positive for desmin. The use of other muscle markers such as muscle specific actin (MSA), myosin smooth muscle heavy chain (SMHC), cadesmon, and calponin were studied in some cases and all showed positive result[2]. The immunohistochemical studies that reported the negative result included S100, CD34, EMA, HMB45, cytokeratin, CD 99, CD31, CD68, Factor VIII, Factor XIII, GFAP, c-kit, CD10, CD23, AFP, NSE, ER, and PR[2].

4. Pathogenesis: Most published reports demonstrated EBV within smooth muscle tumors in HIV-infected patients or in organ transplant patients[1-13,15-19,21-23,25,28,29,32-37]. This was proven by positive EBER in nearly all cases. Some reports used immunohistochemical study for EBNA and PCR in addition to EBER and showed positive result. Immunohistochemical study for Epstein-Barr virus latent membrane protein-1 (LMP-1) was also performed in some cases[9,14,21,22,25] and most showed negative result. In one report case, the tumor showed negative result for both LMP-1 and EBER[14], however PCR was not done in the presented patient. One study detected positive level of anti-EBV antibodies including IgG and IgM in the serum[5] and another study showed EBV in peripheral-blood mononuclear cells[29]. This indicated past or present EBV infection.

The presence of EBV infection in smooth muscle tumor cells strongly supports a role for this virus in the pathogenesis of this type of tumor in addition to nasopharyngeal carcinoma and some type of lymphoma.

Furthermore, some studies reveal that smooth muscle tumor arising in immunocompetent patients does not demonstrate an association with EBV[22,29,33].

5. Treatment: Historically, surgery with negative surgical margin has been the mainstay of treatment. However, in some cases or in incomplete resection, radiation therapy has also been used as an adjunct to surgical resection to maintain local control of the tumor[1]. In unresectable location of tumor or in patients with multiple lesions, radiotherapy or systemic chemotherapy has been used, but the efficacy is not known.

6. Prognosis: The histologic features (mitosis, necrosis atypia) of smooth muscle tumors did not correlate well with the clinical outcome[4,5]. Moreover, it did not appear that the patient's age, gender, CD4 cell count, tumor size, location of the tumor, nor the time to tumor presentation following HIV diagnosis have an impact on their outcome[2]. One literature indicated that, even in the face of multiple tumors, mortality was rarely due to the smooth muscle tumor and it revealed that only about 6% of the patients died of the tumor[4], while most were alive with the tumor. Remaining dead patients were due to their underlying disease.

Because this EBV-associated tumor arises in low-immune condition, improving the immune status may reduce the occurrence of the tumor, improve remission, and reduce the recurrence rate.

In the literatures that study smooth muscle tumor of leiomyosarcoma type[2,4], EBV-associated leiomyosarcoma appears to be much less aggressive than non EBV-associated leiomyosarcoma that often progresses with hematogenous spread and distant metastasis.

Conclusion

Smooth muscle tumor should be one of the differential diagnoses when the HIV-infected patient presented with masses in any location of the body. This also includes patients with other immunosuppressive conditions.

The occurrence of the tumor in these immunosuppressive patients shows strong association with EBV infection. Multiple locations of the tumor in one patient usually occur.

Treatment in operable cases, complete resection is the first choice. Radiotherapy or chemotherapy is the choice in inoperable cases.

The prognosis is rather good. Most cases do not die due to this tumor.

Potential conflicts of interest

None.

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กรณีศึกษา ผู้ป่วยติดเชื้อเอชไอวีที่เป็นเนื้องอกชนิดกล้ามเนื้อเรียบในสมอง ซึ่งมีความสัมพันธ์กับการติดเชื้ออีบีวี

สลิล ศิริอุดมภาส, ชลศณีย์ คล้ายทอง

รายงานนี้เป็นกรณีศึกษาผู้ป่วยติดเชื้อเอชไอวีที่เป็นเนื้องอกชนิดกล้ามเนื้อเรียบในสมอง โดยการเกิดเนื้องอกชนิดนี้พบว่ามีความสัมพันธ์กับการติดเชื้ออีบีวี ซึ่งในกรณีนี้ได้รับพิสูจน์ด้วยการตรวจหา EBV-encoded RNA (EBER) โดยเทคนิควิธี in situ hybridization และจากการรวบรวมข้อมูลจากรายงานต่าง ๆ พบว่าเนื้องอกชนิดกล้ามเนื้อเรียบที่เกิดขึ้นในสมองนั้นมีโอกาสเกิดขึ้นได้น้อยมากอย่างยิ่ง โดยผู้ป่วยส่วนใหญ่เป็นผู้ที่ติดเชื้อเอชไอวี รวมทั้งพบว่ามีความสัมพันธ์กับการติดเชื้ออีบีวีเช่นเดียวกัน
