Multiple Smooth-Muscle Neoplasm and Thyroid Carcinoma in an Adult with AIDS

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At present, new diseases associated with human immunodeficiency virus (HIV) infection continue to be recognized (1–4). The tumor of smooth-muscle origin has recently been introduced to this entity. The first report of a smooth-muscle tumor arising in children with AIDS was published in 1990 (5). The same kind of tumor in an adult with AIDS was reported in 1992 (1). Recently, further evidence of smooth-muscle tumors associated with Epstein–Barr virus (EBV) infection in AIDS has been described (2–4, 6). The nature of the reported smooth-muscle tumors included both benign (leiomyoma) and malignant (leiomyosarcoma) tumors. In the present study, we report an additional rare case of an adult with HIV infection and EBV-positive, multiple smooth-muscle neoplasms of the thoracic wall, lung and adrenal gland. To the best of our knowledge, this is the first reported case of an AIDS patient with an EBV-positive, primary smooth-muscle neoplasm in the thoracic wall. Another remarkable finding is that of papillary thyroid carcinoma occurring in the same relatively young male patient.

The pathogenesis of the smooth-muscle neoplasm and thyroid carcinoma may be related to the immunodeficiency state or may occur by chance.

Case report. The patient was a 22-year-old Japanese man diagnosed with hemophilia A in 1978 when he was 6 years old. In 1985 he was found to be HIV positive when he was 13 years old. Then he developed AIDS at the age of 18 years. Symptoms of diarrhea, fever, weight loss, herpes zoster infection and systemic lymph adenopathy appeared. His CD4 T-cell counts declined steadily from 400/cu mm (normal range 500–1400/cu mm) in January 1987 to 100/cu in January 1990 and to 10/cu mm in March 1994. The bacterial culture of the feces tested positive for atypical mycobacteria. He also had chest pain and abdominal pain. X-rays and computed tomography (CT) showed a tumor shadow in the left chest wall and multiple low-density areas in the liver. He died of systemic mycobacterial infection, which was proved through an autopsy examination.

Material and Methods. The autopsy specimens were fixed in 10% formalin and processed in the prescribed way for paraffin embedding. Sections of 5 μm thickness were stained with hematoxylin and eosin (HE). Some were performed with periodate-Schiff's (PAS), alcian blue, Grocott's and Ziehl-Neelsen stain.

Immunohistochemical studies were performed on selected paraffin sections. The antibodies used are presented in Table 1. The indirect peroxidase or avidin-biotin-peroxidase technique was used.

A polymerase chain reaction (PCR) study was used to detect EBV DNA. DNA was extracted from the tumor tissue according to the method described by Sato et al. (7), with some modifications. The amplification of DNA was done using Perkin Elmer Cetus PCR 2000 in the mixture of 50 μl containing 1 unit of Taq polymerase (Takara Co.). The procedure was as follows: 40 cycles of reaction were performed under conditions of denaturation for 30 s at 95°C, annealing for 30 s at 54°C and extension for 30 s at 72°C. The oligonucleotide primers used were as follows:

EBV-1: 5′CCAGAGGTAAGTGGACTT3′

EBV-2: 5′CACCGGTGCCTTCTTAGG3′

These primers gave rise to 121 bp amplified products.

RNA in situ hybridization (RISH) was used to detect the EBV (EBER) histologically. Paraffin sections (5-μm thick) of neoplasms were subjected to RISH according to the manufacturer's recommendations, using a fluorescein-conjugated EBV (EBER) oligonucleotide probe (code No. Y0017, DAKO A/S, Denmark). Hybridization products were detected using mouse monoclonal anti-fluorescein isothiocyanate (FITC) (DAKO) and rabbit polyclonal antimouse antibodies conjugated with alkaline phosphatase. A substrate solution of 5-bromo-4-chloro-3-indoyl phosphate (BCIP) and chromogen of nitroblue tetrazolium (NBT) was used to detect EBER signals. Positive staining was identified under the light microscope as dark brown granules at the site of hybridization.

Results. Pathological findings. The notable features of this case are smooth-muscle tumors found in the following organs: 1) in the thoracic wall (Fig. 1a). This tumor was a 2.5 cm round mass and completely movable without any difficulty. The cut surface was shown in Fig. 1b; 2) in the left lung, being multiple, and sized 0.3–0.6 cm; 3) in the medulla of the right adrenal gland, a 1.0 cm round, well-circumscribed mass with incomplete capsulation. The surrounding adrenal cortex was compressed and atrophied. Histologically, the tumors were well differentiated (Fig. 2a and b).

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Table 1

Immunohistochemistry of tumors in the liver, thoracic wall, lung and adrenal gland

Antibody	Source	Liver tumors	Thoracic wall	Lung	Adrenal gland
LCA	DAKO	+++	−	−	−
UCHL-1 (CD45)	DAKO	−	−	−	−
MT-1	Bio-Science	−	−	−	−
MB-1	Bio-Science	++	−	−	−
CD3	DAKO	−	−	−	−
L-26 (panB)	DAKO	+	−	−	−
LN-1 (CDw75)	Histoclone (Nichirei)	++	−	−	−
LN-2 (CD74)	Histoclone (Nichirei)	−	−	−	−
Ki-1 (CD30)	DAKO	−	−	−	−
k-chain	DAKO	P	−	−	−
λ-chain	DAKO	−	−	−	−
Vimentin	DAKO	+	+	−	−
Cytokeratin	DAKO	−	−	−	−
S-100	DAKO	−	−	−	−
Desmin (D33)	DAKO	−	+	+	+
α-SMA	DAKO	−	+++	+++	+++
HHF35 (Muscle actin)	DAKO	−	++	++	++
Factor-VIII	DAKO	−	−	−	−
CD34	DAKO	−	−	−	−
CD31	DAKO	−	−	−	−
Kp-1 (CD68)	DAKO	−	−	−	−

$-$ = $<10\%$ of positive neoplastic cells; + = 10–30% of positive neoplastic cells; ++ = 30–70% of positive neoplastic cells; +++ = $>70\%$ of positive neoplastic cells.

Disseminated mitotic activities were also observed in the tumor. The number of mitotic figures was counted in 3 sets of 10 high-power fields (about 1 mm^2). There was less than 1 mitotic figure per 1 mm^2 in each tumor. The adrenal tumor was composed of spindle cells in the peripheral area and pleomorphic round and relatively large cells with moderate atypia in the center. Other findings in this case were: 1) papillary carcinoma of the thyroid gland, left lobe, 0.8 cm in greatest dimension; 2) multiple malignant lymphoma of the liver, diffuse, mixed small and large cell histologically; 3) systemic mycobacterial infection in systemic lymph nodes, spleen, alimentary tract, lung, liver, kidney, digestive tract and bone marrow, including the tumors.

Immunohistochemistry. The tumors of the thoracic wall, the lung and the adrenal gland were positive (Fig. 2c) for α-SMA (alpha smooth-muscle actin), HHF35 and desmin, and negative for von Willebrand factor (Factor VIII-related antigen), CD_{34} and S-100 (see Table 1). Therefore, tumors of a smooth-muscle origin were concluded. The malignant lymphoma of the liver was positive for LCA, partial tumor cells positive for MB-1, a few cells positive for L-26 and some large cells positive for LN-1 (see Table 1). B-cell lymphoma was identified.

RNA in situ hybridization (RISH). Most nuclei of smooth-muscle neoplastic cells in the thoracic wall, the lung and the adrenal gland were positive for hybridization signals of EBERs, whereas the nuclei of adjacent tissue were negative (Fig. 3). The nuclei of the lymphoma cells of the liver were also positive for hybridization signals of EBERs. No hybridization signals of EBERs were detected in the papillary thyroid carcinoma.

Polymerase chain reaction (PCR). DNA from the smooth-muscle neoplasms of the adrenal gland, lung as well as thoracic wall and lymphoma of the liver gave PCR products of 121 bp upon amplification with the EBV-specific primers. DNA from the thyroid carcinoma did not give the above PCR products.

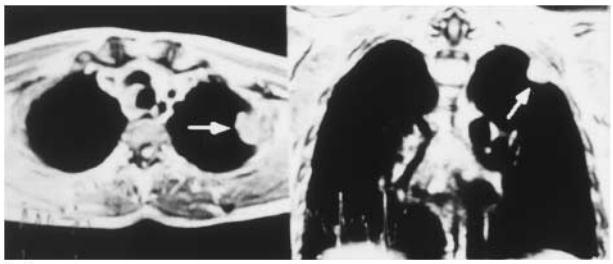
Discussion. The first case of a smooth-muscle tumor in an adult with HIV infection was reported in 1992 (1). Until now, only 6 isolated cases of smooth-muscle tumors in adults with AIDS have been reported (1, 3, 5, 6, 8, 9). Among them, 3 cases showed EBV positivity in the tumor. The locations of the smooth-muscle tumors varied (1). The reported cases suggest a multicentric origin, including: stomach, small bowel, colon, liver, gallbladder, spleen, abdominal lymph nodes, lung, spine, spinal epidural cavity and adrenal gland. The thoracic wall has been added as a new anatomic site with our case. This is the first report showing primary leiomyoma located in the thoracic wall. It suggests that smooth-muscle neoplasms may develop occasionally in unusual sites in patients with AIDS.

The pathological features of the smooth-muscle neoplasms were not predictive of biologic behavior. The tumors in our case were from 0.3 to 2.5 cm in greatest dimension and were composed of fascicles of spindle cells that have fine chromatin, inconspicuous nucleoli, minimal atypia and focal mild pleomorphism as well as low mitotic rate. No lymphatic or venous invasion was found in the tumors, although, histologically, some tumor cells were found infiltrating the fibrous capsule and adjacent tissue. According to the published critera (10, 11), the neoplasms were of benign or uncertain malignant potential. The variation in histological aggressiveness from benign to over malignant was also noted to be the same by others (12). A tumor of uncertain malignancy was suggested by some authors (13) to interpret the bland-looking smooth-muscle tumors.

The multiple smooth-muscle neoplasms of our case were considered to be multiple originated. However, we cannot exclude the possibility that two of the smooth-muscle neoplasms are metastases from the third one, yet the EBV signals were identified in most nuclei of all the multiple tumors. The oncogenesis of such neoplasms remains uncertain. The report of multiple smooth-muscle tumors which developed during immunosuppression in patients who underwent an organ transplantation may suggest that immunodeficiency states of varying etiology could predispose patients to the development of such neoplasms. It has recently

been reported that EBV infection in patients with an immunodeficiency state can produce smooth-muscle tumors (14). In our case, EBERs were also detected in the neoplastic cells, located in the nuclei. The evidence of EBV in the tumor cells strongly supports our belief that EBV may play a significant role as a co-factor in the development of the tumors, although we cannot determine whether the EBV infection occurs before or after neoplastic transformation.

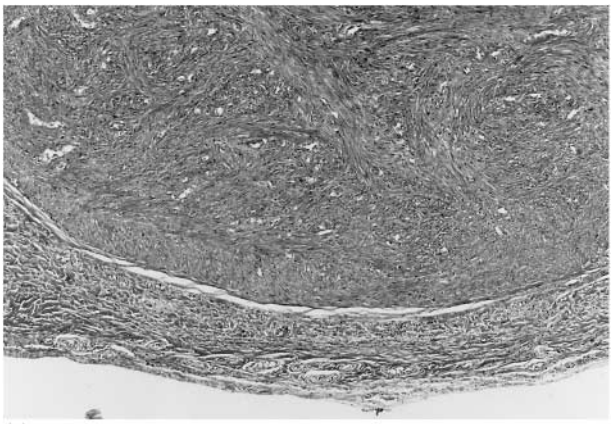
The thyroid papillary carcinoma was found by chance in the systemic autopsy. It is well known that this tumor is usually found in the third-to-fifth decades with a 2 to 3:1 female preponderance. Therefore, this was also a rare tumor occurring in a 22-year-old male patient associated with AIDS. The PCR and RISH results show that no EBV signals were detected in the nuclei of the tumor. At present, we cannot tell whether there is any relationship between thyroid carcinoma and an AIDS state.



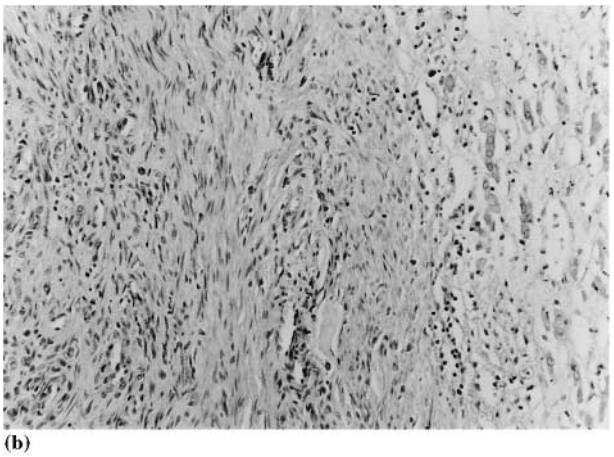
(a)

(b)

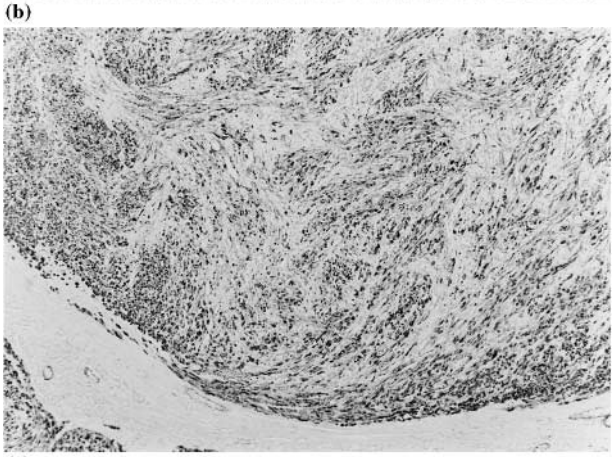
Fig. 1. a) Computed tomography (CT) scan showing a 2.5 cm round mass adhered to the left second rib of the chest, covered by pleura and herniated into the thoracic cavity (indicated by arrow). b) Cut surface of the tumor showing lobate, white and firm with clear margin and capsule.



(a)



(b)



(c)

Fig. 2. Smooth-muscle tumor in the thoracic wall (2a) and adrenal gland (2b) showing facicles of spindle cells with eosinophilic fibrillary cytoplasm, well differentiated (HE, original magnifications $\times$ 160 (2A) and $\times$ 250 (2b). The multiple soft tissue tumors of the thoracic wall (2c, original magnifications $\times$ 160) showing positive for the antibody of α-SMA by the indirect immuno-peroxidase stain method.

Malignant lymphoma is a very common disease found in AIDS patients. The characteristics of the lymphoma of our patient were manifested as follows: 1) multiple nodular lesions in the liver; 2) mixed, small and large cell (pleomorphism) type; 3) B-cell lymphoma, tumor cells showing various immunohistochemical expression for several B-cell markers; 4) EBV positive, detected by PCR and RISH.

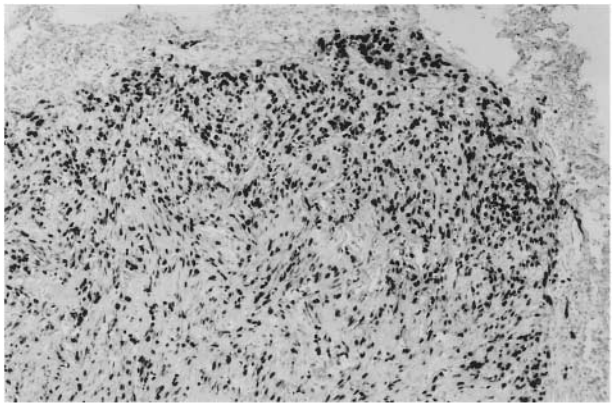


Fig. 3. Nuclei of the smooth-muscle neoplastic cells are positive for hybridization signals of EBERs (RISH, original magnifications × 250). Positive tumor cells were also found in the fibrous capsule and infiltrating to the adjacent tissue.

In addition, atypical mycobacteria were found in most of the tumors and organs (spleen, lymph nodes, lung, liver, digestive tract and bone marrow) especially in the lymphoid organs in which the large cells were packed with a large number of bacilli. The proliferation of abundant bacilli in most organs and tissues may cause further deterioration of the systemic function, resulting in the death of the patient.

In conclusion, there were three different primary neoplasms, both benign and malignant, found in this case. The decreased immune surveillance contributes to the pathogenesis of smooth-muscle neoplasms and lymphoma in such patients. EBV may play a role as a co-factor. It was unusual to find this thyroid papillary carcinoma occurring in this relatively young male patient with AIDS. Mycobacterial infection is another opportunistic infection besides EBV and is a life-threatening complication in patients with AIDS. The patient in this case lived a relatively long life (4.5 years) after the onset of AIDS. Severe mycobacterial infection led to this patient's eventual death.

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