Risk of Bronchioloalveolar Carcinoma in Patients with Human T-cell Lymphotropic Virus Type 1 (HTLV-I): Case-control Study Results

Hiroaki Nomori, MD, PhD, Takeshi Mori, MD, PhD, Kenichi Iyama, MD, PhD, Tatsuya Okamoto, MD, PhD, and Mitsuhiro Kamakura, MD, PhD

Background: Human T-cell lymphotropic virus type 1 (HTLV-I) causes not only adult T-cell leukemia (ATL) but also HTLV-I associated T-cell bronchioloalveolitis, which is often chronic and subclinical. We have experienced eight HTVL-I carriers with bronchioloalveolar carcinoma, which is known to arise from bronchioloalveolar pneumocytes. This case-control study clarified the risk of bronchioloalveolar carcinoma in HTLV-I carriers.

Materials and Methods: During the past four years, 212 lung cancer patients were examined for serum anti-HTLV-I antibody. They underwent surgical treatment for lung cancer at Kumamoto University Hospital. Of these, 8 (4%) were HTLV-I carriers. As controls for this case-control study, we selected 24 HTLV-I negative-lung cancer patients (1:3 case-control ratio) matched for sex, age, and smoking status. The distributions of histological types of lung cancer were compared between the case (HTLV-I positive) and control (HTLV-I negative) groups.

Results: Histological types of the 8 HTLV-I carriers were bronchioloalveolar carcinoma in 6 patients and adenocarcinoma with bronchioloalveolar carcinoma component in 2. The prevalence of bronchioloalveolar carcinoma in HTLV-I carriers, 6 of 8 (75%), was significantly higher than the 6 of 24 (25%) in HTLV-I negative patients ($p = 0.02$). The prevalence of bronchioloalveolar carcinoma or adenocarcinoma with bronchioloalveolar carcinoma component in HTLV-I carriers, 8 of 8 (100%), was also significantly higher than the 13 of 24 (54%) in HTLV-I negative patients ($p = 0.02$).

Conclusion: HTLV-I might be one risk of bronchioloalveolar carcinoma, probably because of inflammatory and/or immunologic responses involving bronchioloalveolar pneumocytes.
Introduction

Human T-cell lymphotropic virus type 1 (HTLV-I) is a human retrovirus known to cause adult T-cell leukemia (ATL).

This viral infection is endemic in Caribbean countries, South America, Africa, and southwestern Japan. The incidence of HTLV-I carriers is known to be dependent on geographic location, and as such, it is reportedly as high as 16% in the southern islands of Japan. This virus has been reported to be associated with several non-malignant disorders, such as HTLV-I associated myelopathy (HAM), HTLV-I associated uveitis (HAU), and HTLV-I associated bronchioloalveolitis (HAB). Actually, HAB is a chronic T-cell bronchioloalveolitis, which shows an interstitial pneumonia-like shadow on chest X-ray, an increased total cell count, and an increased proportion of T-cells in bronchoalveolar lavage (BAL) fluid, despite normal chest X-ray findings and pulmonary functions of the patient. Although HAB is often observed in patients with HTLV-I associated myelopathy (HAM), it is also observed in asymptomatic HTLV-I carriers. However, no reports have described whether HTLV-I might cause lung cancer.

During the past 4 years, we diagnosed bronchioloalveolar carcinoma (BAC) in 8 patients who were carriers of HTLV-I. BAC is distinct from other lung cancers: it is usually a carcinoma in situ, characterized by tumor cell growth along alveolar septa without stromal, vascular, or pleural invasion. Although most lung cancers originate from the bronchial epithelium, BAC has been considered to arise from bronchioloalveolar pneumocytes. We hypothesize that chronic and subclinical HAB in HTLV-I carriers promote tumorigenesis of bronchioloalveolar pneumocytes, thereby causing BAC. Using a case-controlled study, we evaluated the risk of BAC in HTLV-I carriers.

Materials and Methods

Eligibility

The study protocol, designed to examine serum anti-HTLV-I antibody in patients with lung cancer who had undergone surgical resection in Kumamoto University Hospital, was approved by the Ethics Committee of Kumamoto University School of Medicine.

Examination of serum anti-HTLV-I antibody

The titers of serum anti-HTLV-I antibody were examined using particle agglutination (PA) kits (Serodia; Fujirebio Inc., Tokyo, Japan). For this study, PA positivity was defined as agglutination at ≥16-fold serum dilution.

Study subjects

During April 2005 – March 2008, 381 patients with primary lung cancer underwent surgical treatment at Kumamoto University Hospital. Of these, 212 patients were examined for serum anti-HTLV-I antibody. Of the 212 patients, 8 (4%) were HTLV-I positive; the other 204 were negative. For the case–control study, 24 HTLV-I negative patients (1:3 case-control ratio) matched for sex, age (±3 yr), and smoking status served as controls. For each HTLV-I positive case, 3 HTLV-I negative controls were selected from 204 HTLV-I negative patients who had undergone surgical treatment on the dates nearest to those of the 8 HTLV-I positive patients.

The distributions of histological type of lung cancer were compared between the case group (HTLV-I positive) and control group (HTLV-I negative). The family histories of lung cancer in first-degree and second-degree relatives were also compared between the two groups.
The histological diagnosis of lung cancer was classified according to the World Health Organization (WHO) system.13, 14) Adenocarcinoma was further subclassified into adenocarcinoma with and without a BAC component. The histological sections were reviewed by a pathologist (K.I.) who had 35 years of experience in pathological diagnosis and who was unaware of the clinical data of the patients.

Statistical analysis

All data were analyzed using Fisher’s exact test. Differences between the cases and controls with p values less than 0.05 were regarded as significant.

Results

Table 2 shows characteristics of the 8 HTLV-I carriers and 24 HTLV-I negative controls. The HTLV-I carriers included 4 males and 4 females, of whom 5 had never smoked, and 3 were current smokers. The mean age of both groups was 67 ± 7 yr. Their histological types were BAC in 6 patients and adenocarcinoma with a BAC component in 2. Of them, 4 patients had a family history of lung cancer among first-degree and second-degree relatives. None of the 8 HTLV-I carriers showed abnormal lesions on chest CT, other than lung cancers. On the other hand, the histological types of the 24 control patients were BAC in 6, adenocarcinoma with a BAC component in 7, adenocarcinoma in 10, and squamous cell carcinoma in 2. The family history of lung cancer was positive in 7 of the 24 controls (29%).

Table 3 presents distributions of BAC in HTLV-I positive and negative patients. Of the 8 HTLV-I positive patients, 6 (75%) had BAC, of which the frequency was significantly higher than the 6 of 24 (25%) HTLV-I negative patients (p = 0.02).

Table 4 presents distributions of BAC or adenocarcinoma with a BAC component in HTLV-I positive and negative patients.
negative patients. All 8 HTLV-I positive patients (100%) had a BAC component. The frequency was significantly higher than the 13 of 24 (54%) HTLV-I negative patients ($p = 0.02$).

The family history of lung cancer did not differ significantly between the two groups ($p = 0.3$).

**Discussion**

While it has been reported that a βretrovirus-Jaagsiekte sheep retrovirus- causes pulmonary adenocarcinoma in sheep, which resembles human BAC,$^{16}$ none of the virus has been reported to cause human lung cancer. Our case–control study showed a significantly high risk of BAC in HTLV-I carriers. Compared with other lung cancers, BAC is a distinct entity, especially in terms of tumorigenesis: BAC arises from bronchioloalveolar pneumocytes, whereas, most other lung cancers are derived from bronchial epithelium. Our data show that bronchioloalveolar pneumocytes in HTLV-I carriers are more likely to develop BAC than the pneumocytes in non-carriers are.

The age of BAC patients among HTLV-I carriers was $67 \pm 7$ yr, which was the general age of lung cancer patients, casting doubt on whether or not HTLV-I is an actual cause of BAC. However, the mean age of ATL, which is caused directly by HTLV-I, was reported as about 60 years old because most HTLV-I infections are chronic. Therefore, if we assume that HTLV-I is causing BAC, it stands to reason that the mean age of HTLV-I carriers with BAC is about 60 years of age.

Although clinical or subclinical HAB is reportedly often observed in patients with HAM,$^{9-11}$ subsequent reports have described that HAB is also observed in asymptomatic HTLV-I carriers.$^{12}$ Mori et al. reported that the percentage of T-cells in BAL of HTLV-I carriers correlated significantly with the copy number of the HTLV-I proviral DNA load in peripheral blood mononuclear cells, suggesting an important role of HTLV-I proviral DNA load in the development of HAB in asymptomatic HTLV-I carriers.$^{17}$ Although we did not examine BAL in our 8 HTLV-I carriers, chronic and subclinical HAB might have been present in their lung tissues.

Tumorigenesis in lung cancers is known to result from nuclear injury, including DNA translocation, activation of proto-oncogenes, or inactivation of tumor suppressor genes. Reportedly, BAC develops in transgenic mice overexpressing c-myc and epidermal growth factor (EGF).$^{13}$ Results of the present study suggest that chronic and subclinical HAB in HTVL-I carriers could cause these genetic alterations in bronchioloalveolar pneumocytes, thereby resulting in BAC.

A weakness of this study is the lack the incidence of lung cancer or BAC in a large population of HTLV-I carriers. Although no reports have described the incidence of lung cancer in HTLV-I carriers, we consider it difficult to demonstrate a higher incidence of BAC in HTLV-I carriers than in HTLV-I non-carriers for the following reasons. (1) Although HTLV-I directly causes ATL, even the ATL incidence in HTLV-I carriers is reportedly only between 1 and 5%. (2) While HTLV-I might be exhibiting its effect on BAC indirectly through inflammatory and/or immunologic responses involving bronchioloalveolar pneumocytes, it is difficult to demonstrate a significantly higher incidence of BAC in HTLV-I carriers than in non-carriers, even in a large population, because of its little incidence.

The next step is to demonstrate inflammatory conditions fundamentally in lung tissues of HTLV-I carriers with BAC.

**References**

1) Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, et al. Detection and isolation of type C retrovirus

---

**Table 4** Distribution of bronchioloalveolar carcinoma or adenocarcinoma with bronchioloalveolar carcinoma in HTLV-I positive and negative patients

<table>
<thead>
<tr>
<th>HTLV-I</th>
<th>Histological type</th>
<th>BAC or Ad with BAC</th>
<th>NSCLC without BAC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>11</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>11</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

BAC, bronchioloalveolar carcinoma; Ad, adenocarcinoma

Fisher’s exact test: $p = 0.02$


