Letter to the Editor

Does an Epstein-Barr Viral Infection Influence the Pathogenesis of a Primary Pulmonary B-Cell Lymphoma?

The Epstein-Barr virus (EBV) is an ubiquitous herpesvirus that can infect and transform B-lymphocytes. It has been reported that the lung is a major EBV reservoir [9] and that various lymphoproliferative disorders of the thorax, such as lymphomatoid granulomatosis (LYG)/angiocentric immunoproliferative lesions (AIL), lymphocytic interstitial pneumonia (LIP), and pyothorax-associated pleural lymphoma are associated with an EBV infection [1, 3, 4]. However, in a few cases of primary pulmonary lymphoma, the EBV genome was not detected by using polymerase chain reaction [7]. Therefore, to determine whether an EBV infection is related to the pathogenesis of a primary pulmonary lymphoma, we have investigated lung tissue sections taken from 12 patients with a primary pulmonary lymphoma (a lobectomy in 9 patients and an open lung biopsy in 3) by using in situ hybridization with EBV-encoded small RNA-1 (EBER-1), which is abundant in latently infected cells [2, 6].

All 12 patients lacked an underlying pulmonary, hematologic, and/or autoimmune disorder. Pathologically, the lymphomas were diagnosed as low-grade B-cell lymphomas (CD20+, CD45RO-, composed of small to intermediate-sized lymphoid cells) [8, 10]. The tumors frequently manifested typical morphologic features of mucosa-associated lymphoid tissue (MALT) lymphoma [5], such as lymphoepithelial lesions and reactive follicles. The EBV in situ hybridization studies were performed by using a 30-bp oligonucleotide probe complementary to a portion of the EBV transcripts EBER-1 [2, 6]. Briefly, sections 4 μm thick, cut from paraffin-embedded blocks of buffered formaldehyde-fixed tissue, were deparaffinized, dehydrated, predigested with pronase, and prehybridized, after which they were hybridized with digoxigenin-labeled antisense oligoprobe (5’DIG-AAACATGCGGACCACCAGCTGGTACTTGA-3’) overnight. After washing, the sections were incubated with the antidigoxigenin antibody. Next, they were again washed, and the color products were then developed by the nitroblue tetrazolium chloride-5-bromo-4-chloro-3-indolyl-phosphate system. Serial sections of each sample were hybridized with a sense probe (5’DIG-TCAAGTACCAGCTGGTGTCGCCCAT-GTTTT-3’), which served as a negative control for an EBER-1 signal.

In all 12 primary pulmonary B-cell lymphoma cases, the signal for EBER-1, using the antisense probe, was negative (Fig. 1A); the signal was also negative
when the slide was hybridized with the sense probe. A positive control case with B-cell lymphoma with a hereditary immunodeficiency syndrome that had been known to be infected with EBV showed a clearly positive signal with the antisense probe (Fig. 1B) and a negative response with the sense probe. These findings suggest that an EBV infection is not associated with a primary pulmonary B-cell lymphoma.

It has been found that a primary pulmonary lymphoma mainly shows a B-cell immunophenotype and that the majority of B-cell lymphomas are thought to be MALT lymphomas [8]. With regard to MALT lymphomas of the salivary gland, the thyroid, and the stomach, it has been suggested that the acquired MALT in these sites secondary to autoimmune diseases, i.e., Sjögren’s syndrome or Hashimoto’s thyroiditis, or to an infection, such as Helicobacter gastritis, may form the substrate for the development of a lymphoma [5]. As for the lung, however, the etiology of MALT lymphomas remains uncertain. These data indicate that a primary pulmonary B-cell lymphoma is not associated with an autoimmune disorder or an EBV infection of the lung. Further studies are required to clarify the precise contribution of a pulmonary infection in the pathogenesis of primary pulmonary B-cell lymphoma.

Acknowledgment. This study was a multi-institutional work conducted by the Japan National Chest Hospital Study Group for Lung Cancer.