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Original contribution

Enteropathy-associated T-cell lymphoma—a clinicopathologic and array comparative genomic hybridization study☆,☆☆

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Summary According to the new World Health Organization classification system, there are 2 types of enteropathy-associated T-cell lymphoma. Type 1 is associated with celiac disease and accounts for the majority of cases in Western countries, whereas type 2 is not associated with celiac disease. To characterize enteropathy-associated T-cell lymphoma types in Korea, we carried out clinicopathologic and immunophenotypic analyses of 8 Koreans with enteropathy-associated T-cell lymphoma and investigated genomic profile using array comparative genomic hybridization. The tumors involved the small intestine in 5 patients and the colorectum in 3 patients. Two patients carried an HLA DQB1∗0302 allele that corresponds to HLA DQ8. None of the patients had gluten-sensitive malabsorption syndrome. Intraepithelial lymphocytosis was observed in all patients. The sizes of the tumor cells were small or small-to-medium in 7 cases and medium-to-large in 1 case. The immunophenotypes of the tumor cells were CD4−CD8+CD56+ in 4 cases, CD4−CD8+CD56− in 1 case, CD4−CD8−CD56+ in 2 cases, and CD4−CD8−CD56− in 1 case. Array comparative genomic hybridization analysis showed that chromosome 9q33-q34.1 gain was present in 4 (80%) of the 5 cases examined. Other recurrent genomic alterations were gain of 6p21.1-21.31 (3/5, 60%), gain of 19q (2/5), and the loss of 3p12.1-p12.2 (2/5) and 3q26.31 (2/5). These results suggest that the most prevalent type of enteropathy-associated T-cell lymphoma in this geographic region is type 2, and the genetic changes associated with it are similar to those in Western countries.

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1. Introduction

Enteropathy-associated T-cell lymphoma (EATL) is defined as an intestinal lymphoma of intraepithelial T lymphocytes [1,2]. It is uncommon in most parts of the world, but has been observed with increasing frequency in areas in which there is a high prevalence of celiac disease, particularly in Northern Europe. The characteristics of celiac-associated EATL have been well described. This disease commonly involves the jejunum and usually presents as a tumor consisting of large lymphoid cells. Celiac-associated EATL patients have a history of gluten-associated malabsorption or histologic evidence of enteropathy (villous atrophy, crypt hyperplasia, or intraepithelial T lymphocytosis [IEL]) in the small intestinal mucosa adjacent to the tumor. The degree of enteropathy is highly variable and may consist only of an increase in the number of intraepithelial lymphocytes. The neoplastic cells are cytotoxic T lymphocytes, usually of the CD4−CD8−/+ immunophenotype [3-6].

Recent studies have identified another form of EATL, which is not associated with celiac disease [3-6]. The tumor cells of this form of EATL differ from those of celiac-associated EATL and consist of monomorphic small cells with clear cytoplasms. The adjacent intestinal mucosa shows histologic evidence of enteropathy. The immunophenotype of the monomorphic form of EATL is CD4−CD8+CD56+ [3-6].

The 2 types of EATL are associated with similar, but not identical, genetic alterations. A recent array comparative genomic hybridization (CGH) study showed that complex gains of 9q31.3-qter are frequent in both types.

The prevalence of these types of tumor may differ between geographic regions. The 2008 World Health Organization (WHO) classification system states that type 1 EATL accounts for the majority of EATL cases (80%-90%) [1]. However, intestinal T-cell lymphomas associated with celiac disease are very rare in our country. Because celiac disease is uncommon in Far East Asia [7], some characteristics of EATL in this region may differ from those in Western countries even though they have morphologic similarities. To test this hypothesis, we analyzed the clinicopathologic findings and genomic profiles of 8 Korean cases of EATL.

2. Materials and methods

The cases were selected in accordance with the modified WHO criteria [1]. The inclusion criteria were as follows: (1) intestinal T-cell lymphoma, (2) histologic indicators of enteropathy: IEL (≥40 lymphocytes per 100 epithelial cells), and (3) a cytotoxic phenotype of CD4−CD8+ or CD4−CD8−.

Twelve cases of intestinal T-cell lymphoma were identified using the surgical pathology files of the Department of Pathology of Samsung Medical Center for 1995 to 2007. Of the 12 cases, 8 were selected and 4 were excluded. The reasons for exclusion were as follows: no IEL (1), IEL present but of the CD4 phenotype (1), and no tissue section available for analysis (2). The study was approved by the Institutional Review Board in accordance with the Declaration of Helsinki.

2.1. Immunophenotype studies

Immunohistochemical analysis of paraffin-embedded tumor sections from all 8 cases was performed using monoclonal and polyclonal antibodies against the following lineage-specific or lineage-characteristic antigens: CD3 (Dakopatts, Copenhagen, Denmark), CD20 (Dakopatts), CD56 (Monosan, Uden, the Netherlands), CD4 (Novocastra, Newcastle upon Tyne, United Kingdom), CD8 (Novocastra), βF1 (Endogen, Rockford, IL), and TIA-1 (Zymed, South San Francisco, CA).

2.2. Epstein-Barr virus in situ hybridization

Epstein-Barr virus (EBV) RNA was detected using an in situ hybridization technique. Paraffin-embedded sections (5 μm) were dewaxed using xylene, treated with proteinase K, and hybridized with fluorescein isothiocyanate–conjugated EBER-1 and -2 oligonucleotide probes (Novocastra). After incubation with anti–fluorescein isothiocyanate antibody tagged with alkaline phosphatase, slides were covered with nitroblue tetrazolium, 5-bromo-4-chloro-3-indolyl phosphate, and 1 mol/L levamisole. For negative controls, we used EBV-negative lymphoid tissues and the hybridization mixture without EBV oligonucleotides.

2.3. Array CGH

DNA was extracted from paraffin blocks containing tumor tissue. Labeling, array fabrication, hybridization, and analysis were performed as described previously [8]. The array CGH, ACC Version 5.0, consisted of 2304 BAC/PAC clones from libraries RP-11 and -13 for BAC clones and libraries RP-1, -3, -4, and -5 for PAC clones. These clones were obtained from the BAC/PAC Resource Center of the Children's Hospital of Oakland Research Institute in Oakland, CA (http://bacpac.chori.org/). The names of the clones and their locations on chromosomes are listed with the raw data presented in Supplemental Information 1. BAC and PAC clones were aligned with each chromosome on the basis of Ensembl Genome Data Resources (release 40, http://www.ensembl.org/) or the National Center for Biotechnology Information (Build 36, http://www.ncbi.nlm.nih.gov/). The locations of all clones used for array CGH were confirmed by fluorescence in situ hybridization. Clones with copy number variations among 17 unrelated normal individuals and clones of the sex chromosomes