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Original contribution

Detailed clinicopathological characteristics and possible lymphomagenesis of type II intestinal enteropathy-associated T-cell lymphoma in Japan☆,☆☆

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Summary Twenty-six Japanese cases of type II enteropathy-associated T-cell lymphoma (EATL) were examined. Multiple tumors throughout the small intestine were found in 15 patients (58%) and duodenal and colonic mucosal lesions in 8 and 6 cases, respectively. Histologically, intramucosal tumor spread and a zone of neoplastic intraepithelial lymphocytes (IELs) neighboring the main transmural tumors were detected in 20 (91%) and 17 (77%) of the 22 cases examined, respectively. Inside and outside the IEL zone, some degree of enteropathy with many reactive small IELs and villous atrophy was detected in 11 cases (50%). Immunohistologically, many CD56/CD8-positive small IELs were found in the enteropathic lesions of 4 (36%) and 7 (64%) of these 11 cases. Lymphoma cells expressed tyrosine kinase receptor c-Met, serial phosphorylated (p)–mitogen-activated protein kinase/extracellular signal–regulated kinase, c-Myc, and Bcl2 in 18 (78%), 21 (91%), 11 (42%), and 19 (73%) of the total cases, respectively. By fluorescence in situ hybridization,

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chromosomal loci 7q31 (c-*Met*) and 8q24 (c-*Myc*) were amplified in 11 (65%) and 12 (71%) of the 17 cases analyzed. Gain of 7q31 and c-Met expression were significantly ($P < .01$) higher than in peripheral CD8-positive T-cell or CD56-positive natural killer–cell lymphomas. Enteropathy was seen near the IEL zone in type II EATL, and activation of the c-Met, mitogen-activated protein kinase/extracellular signal–regulated kinase–mitogen-activated protein kinase pathway, and c-Myc–Bcl2–mediated cell survival may play important roles in lymphomagenesis, converting enteropathy to type II EATL. Seven cases in the early clinical stages I and II-1 showed significantly ($P < .01$) better prognoses than did those in the advanced stages. Early detection of the mucosal lesions and tumors may improve patient prognosis.

1. Introduction

Enteropathy-associated T-cell lymphoma (EATL) is a rare disorder most frequently seen in whites of Northern European origin [1]. Approximately 80% of EATL tumors are composed mainly of type I CD30-positive large-cell lymphoma, frequently with multiple diffuse tumors in the small intestine. The remaining cases, classified as type II, are mainly CD56/CD8-positive monomorphic medium-sized lymphoma cells [2]. It is suggested that CD8-positive intraepithelial lymphocytes (IELs) in celiac disease will undergo conversion to CD8-negative, CD30-positive type I EATL, and that the IELs may be the cellular origin of type I EATL [3].

Comparative genomic hybridization (CGH) indicates that common chromosomal alterations in type I EATL and celiac disease are gains of 9q33-34, 1q22-q44, and 5q31-33, whereas gains of 9q3 and 8q24 (c-*Myc*) are typical in type II disease [2,4]. On the other hand, there was no evidence of gains of 9q3, 1q3, or 5q3 by CGH in 20 Japanese type II lesions [5]. Human leukocyte antigen DQB1*02 homozygosities and heterozygosities, which are often found in cases of celiac disease and type I EATL [2], were absent in the 6 type II cases. In East Asia, type II cases were common and had peculiar pathologic and genetic findings [5-7].

The precursor lesions of type II EATL have not been well documented. Celiac disease is characterized by an increase in reactive small IELs with villous atrophy and crypt hyperplasia in the duodenum and intestine [8]. Asian type II cases show prominent tumor epitheliotropism and some increase in small IELs with less enteropathy in the distant mucosal zone [7]. We tried to find lesions with characteristics of enteropathy that could be the precursors of neoplastic IEL zones and type II EATLs.

Celiac disease may be not involved in the etiology of Asian type II EATL cases [5,9]. Various factors can cause enteropathy as a precursor of type II EATL. *Helicobacter pylori* infection and ulcerative colitis induce duodenitis with increased CD8-positive IELs [10,11]. *Helicobacter* infection, especially of the East Asian type, elevates protooncogene c-*Met* signal transduction in epithelial cells, and aberrant c-Met expression contributes to neoplastic transformation of epithelial and B cells via the mitogen-activated protein kinase/extracellular signal–regulated kinase (MEK)–mitogen-activated protein kinase (MAPK) pathway and c-Myc stabilization [12-15]. The c-*Met* gene, located on chromosome 7q31, and its protein are frequently expressed in B-cell and occasionally in T-cell lymphoma [14]. Isochromosome 7q and gain of chromosome 8 are typical in cases of CD56-positive hepatosplenic T-cell lymphoma [16].

We examined the expression of c-MET, MEK, and c-Myc proteins and gain of chromosomal loci 7q31 (c-*Met*) and 8q24 (c-*Myc*) in type II EATL via fluorescence in situ hybridization (FISH). Histologically, enteropathy with rare instances of crypt hyperplasia was found to some extent inside and outside the neoplastic IEL zone in half of the type II cases. We discuss the clinicopathological findings of enteropathy as a possible precursor of type II EATL, with lymphomagenesis via activation of the c-Met, MAPK, and c-Myc pathways as well as the importance of early detection of the mucosal lesions and tumors.

2. Materials and methods

2.1. Case selection and clinical findings

Institutional ethical approval was obtained for this study in compliance with the Declaration of Helsinki. A series of 34 Japanese patients with primarily intestinal T/natural killer (NK)-cell lymphoma were selected. Cases were first classified according to the World Health Organization system of classification [1]; 2 cases consisted of large cell, type I EATL, and 26 were monomorphic medium-sized type II EATL. Six cases were CD56-positive nasal-type NK-cell lymphomas with Epstein-Barr virus–encoded RNAs detected by in situ hybridization. All of the type II EATL cases were seronegative for antibodies against human T-cell lymphotropic virus type 1 and had no Epstein-Barr virus–encoded RNAs–positive lymphoma. No examinations of antiendomysial IgA or antitransglutaminase antibodies were performed because of the low incidence of celiac disease in Japan. Hypoproteinemia was defined as a total protein concentration of less than 6 g/dL in the serum. The tumor stages were classified according to the modified Ann Arbor staging system published by Lugano (cited by d'Amore et al [17]). For the 26 type II EATL cases, the outcome was determined by calculation of the cumulative survival time, and overall survival curves were generated using the Kaplan-