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Original article

The degree of overlap between the follicular dendritic cell meshwork and tumor cells in mantle cell lymphoma is associated with prognosis

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ABSTRACT

This study concerning mantle cell lymphoma (MCL) investigated retrospectively an association between patient prognosis and the percentage of the total number of lymphoma cells found in the follicular dendritic cell (FDC) meshwork, that is, the degree of overlap of lymphoma cells. Two hundred and nine MCL patients were apportioned to grades I–III, in which the CD21-positive FDC meshwork covered ≤50%, 51%–89%, and ≥90% of the tumor area, respectively. Significant differences among the grades (all, $P < 0.01$) were found in the following: duration of disease (from onset of clinical manifestation to diagnosis); clinical staging; extranodal involvement (non-lymphoid organs); histological subtype; and Ki-67 proliferation index (PI). After removing the aggressive variants, the overall survival rates of grade I (n = 92) and II (n = 57) patients were similar. The overall survival rates of grade III (n = 46) patients differed from that of grade I + II patients ($P < 0.01$). The grades negatively correlated with the Ki-67 PI value ($r = -0.234$, $P = 0.001$). At each grade the OSR of patients with Ki-67 PI ≤30% was similar to that of patients with Ki-67 > 30%. In the Ki-67 PI ≤30% group, the OSRs of the patients differed significantly among the grades. In the Ki-67 > 30% group the OSRs of the grades were similar. The results of multivariate Cox regression analysis showed that the degree of overlap, age and Ki-67 PI was the independent prognostic factors of the OSRs of MCL patients. Our data suggests that MCL patients in whom there was a high degree of overlap between the FDC meshwork and tumor area have a better clinical prognosis. The degree of overlap correlates well with the Ki-67 PI, which can be used to predict the prognosis of patients.

1. Background

Mantle cell lymphoma (MCL) is a B-cell neoplasm, with the chromosomal translocation t (11;14) (q13;q32) and upregulation of cyclin D1 and cluster of differentiation (CD)5 proteins [1–6]. MCL accounts for 3–10% of non-Hodgkin's lymphoma cases [1,7]. It occurs mostly in middle-aged to older individuals, with a median age of about 60, there is a male predominance. The most commonly involved site is lymph node. The extranodal sites are frequently involved [1,3,7].

MCL is aggressive with unique biological characteristics, it has been considered a very aggressive and incurable neoplasia. Most patients present with stage III or IV disease at the time of diagnosis [1,3,6,7]. The median survival time of patients is only 3–5 years [1,6,7]. Moreover, some patients with MCL are insensitive to chemotherapy or they relapse easily, with only 1–2 years overall survival time [6,8].

But there are two indolent variants of MCL which are now also well recognized, including leukaemic non-nodal mantle cell lymphoma and in situ mantle cell neoplasia [4–7]. In addition, some of the classical MCL patients had an indolent clinical manifestation. Even if they were not treated immediately after diagnosis, they still had long survival time [5,6]. These patients may be associated with the tumor's low proliferation index (PI) [3,6–8].

It is essential to understand the relevant factors that influence prognosis in MCL, both to assess prognosis and to customize treatment [3,9–13]. We found in our previous work that in MCL the follicular dendritic cell (FDC) meshwork varied in morphology and distribution. In some cases, the FDC meshwork consisted of a diffuse large net or expanded irregular net, covering almost all the tumor cells, and most of these patients' lymph node enlargement has lasted for several years. In most other cases, the FDC meshwork was nodular or fragmentized, and did not encompass all the tumor cells.

The prognostic impact of the proportion of Ki-67-positive nuclei has been already accepted and incorporated into the MCL international prognostic index (MIPI), scoring system of mantle cell lymphoma [3,7,14–16]; Ki-67 PI > 30% associated with adverse prognosis [3,7,14], meanwhile < 10% with indolent course [3,7]. The present study investigated an association between the prognosis of patients and the degree of overlap of the FDC meshwork and tumor cells in MCL. In

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addition, an association between the degree of overlap and the Ki-67 PI was determined. Thus, this study may provide a reference for clinical treatment and prognostic assessment of risk.

2. Materials and methods

2.1. Selection of cases

This study was based on 449 MCL consultation cases operated on at the Pathology Department of Beijing Friendship Hospital/Lymphoma Diagnosis Research Center of Beijing Institute of Clinical Medicine during 2002–2016. In these cases, 209 met the following criteria for inclusion in this study: received a definitive diagnosis of MCL; with the complete clinical and imaging data, and pathological sections; and follow-up information was intact.

Patients with any of the following were excluded from this study: only core or minimal biopsy specimens; repeated biopsies; lacked satisfactory immunohistochemical (IHC) stained sections; previous history of other malignant diseases; concomitant immunodeficiency diseases; with *in situ* mantle cell neoplasia; and leukaemic non-nodal mantle cell lymphoma.

The study was conducted according to the Helsinki declaration. Written informed consent was obtained for each patient prior to surgical procedure. Beijing Friendship Hospital Ethical Committee Approval (2017-P2-127-02) was acquired for the review and analysis of patients' data.

2.2. Grade (or type) criteria

All the MCL cases were checked and diagnosed by three chief or senior pathologists. In the low power lens, the whole tissue section of IHC staining in each case was observed, the pathologists evaluated and recorded the morphological characteristics of the FDC meshwork in all areas of the tumor tissue, displayed by CD21 IHC staining, and the percentage of tumor cells positive for Ki-67.

In addition, the percentage of all lymphoma cells (i.e., positive for CD5 and/or cyclin D1) that were in the FDC meshwork was recorded. This percentage of the total number of lymphoma cells that was found in the FDC meshwork was considered the degree of overlap of lymphoma cells and the FDC meshwork. The degree of overlap was divided into three grades. The cases were apportioned to grades I–III, that is, the FDC meshwork covered $\leq$50%, 51%–89%, or $\geq$90% of the tumor area, respectively. Grades I and II were considered types that were non-completely overlapped, and grade III was the completely overlapped type. The difference in overall survival rates (OSRs) of the patients among the grades of overlap was analyzed. Also determined was the association between grade and the Ki-67 PI, and the OSR of each grade of overlap and Ki-67 PI.

The average of each feature recorded by the pathologists was calculated.

2.3. IHC studies

The primary antibodies and a MaxVision 2 kit, provided by Maixin Biotech (catalog No. KIT-5910/5931, Fuzhou, China) were used for detection of all antigens. Antigen retrieval was performed at high temperature and high pressure using potassium ethylenediaminetetraacetic acid (EDTA; 1 mmol/L, pH 9.0)/citric acid (0.01 M, pH 6.0) antigen retrieval fluid. The primary antibodies and their working dilutions and pretreatment methods are listed in Table 1. Positivity for cyclin D1, BCL-6, and Ki-67 was defined as a demonstrable presence in the nucleus. Positivity of the remaining antibodies depended on observation in the cytoplasm and/or cell membrane. Positive staining of the nucleus, cytoplasm, or the cell membrane was defined as light yellow to brown. In the tumor cells, negative was defined as without color; positive was pale yellow, yellow-brown, or brown stain (weak, standard, and strong, respectively). Images were scanned with NanoZoomer 2.0-RS (L11600-22, Hamamatsu, Japan) whole slide scanner.

Table 1
Primary antibodies used for immunohistochemical staining and their pretreatments.

Antibody	Clone	Dilution	Pretreatment
CD21	EP3093	1:50	EDTA
CD20	L26	1:200	Citric acid
CD3	SP7	1:100	Citric acid
CD5	SP19	1:50	Citric acid
Cyclin D1	SP4	1:100	EDTA
CD10	56C6	Ready to use	EDTA
BCL6	LN22	1:20	EDTA
BCL2	8C8	1:300	Citric acid
CD23	SP23	1:100	Citric acid
Ki-67	MIB-1	1:200	Citric acid

2.4. FISH analysis

FISH analysis was employed for the detection of gene fusion affecting CCND1 (cyclin D1), that is, IGH (immunoglobulin heavy chain)/CCND1, and was observed by fluorescence microscope (Zeiss Imager, M2, German). Specifically, formalin-fixed, paraffin-embedded sections (4 μm) were placed in a 65 °C oven overnight. Sections were pretreated with 0.5 g/L pepsin (Sigma) for 20 min, and hybridization was performed with a IGH/CCND1 dual color dual-fusion translocation probe (Vysis-Abbott, IL, USA) at 37 °C for 18 h. Sections were immersed in 0.3× NP40/0.4× SSC (0.3 M sodium chloride and 0.03 M sodium citrate) solution at room temperature (5 min) and at 73 °C (2 min), counterstained with 10 μL DAPI (4′,6-diamidino-2-phenylindole) solution, and viewed using a fluorescence microscope with filters for DAPI, spectrum green, and spectrum orange.

Two separate red signals and two separate green signals, for $\geq$100 tumor cells, were interpreted as normal mitotic cells. Gene translocation was defined as > 5% of tumor cell nuclei with two fusion yellow signals, a single green signal, and a single red signal.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Co., Armonk, NY, USA). The chi-squared test or Fisher's exact test was used for comparisons of enumeration data, and the two-sided asymptotic or exact value was selected. Correlation was analyzed using Spearman's related analysis (coefficient *r*). The time of overall survival was defined as from the date of diagnosis to the time of the last follow-up or death due to any cause. The survival rate was judged according to log rank statistical analysis, and the survival curve was determined using the Kaplan-Meier method. Univariate and multivariate analysis was performed using the Cox proportional hazard model. The multivariate analysis was conducted using the factors proven significant in the univariate analysis. $P < 0.05$ was considered statistically significant.

3. Results

3.1. FDC meshwork and the regularity of grading

The CD21 staining showed that 95.7% (200/209) of the tumors had the FDC meshwork. Growth patterns of the FDC meshwork were varied, with a loose framework; or a meshwork that was residual or broken; shrunken spherical; nodular; or enlarged irregular or diffuse.

The tumor cells were positive for CD20, CD5, cyclin D1, and BCL-2, but negative for CD3, CD10 and BCL-6. CD23 was weakly positive in 9 cases. The tumor cells were weakly positive for CD21 in 38 cases.

Four cases of CD5 were negative and 7 cases of cyclin D1 were

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