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Original contribution

Hodgkin lymphoma variant of Richter transformation: morphology, Epstein-Barr virus status, clonality, and survival analysis—with comparison to Hodgkin-like lesion☆,☆☆

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Summary Hodgkin/Reed-Sternberg (HRS) cells in the setting of chronic lymphocytic leukemia (CLL) exist in 2 forms: type I with isolated HRS cells in a CLL background (Hodgkin-like lesion) and type II with typical classic Hodgkin lymphoma, a variant of Richter transformation (CHL-RT). The clinical significance of the 2 morphological patterns is unclear, and their biological features have not been compared. We retrospectively reviewed 77 cases: 26 of type I and 51 of type II CHL-RT; 3 cases progressed from type I to type II. We examined clinical features, Epstein-Barr virus (EBV) status, and clonal relatedness after microdissection. Median age for type I was 62 years versus 73 years for type II (P = .01); 27% (type I) versus 73% (type II) had a history of CLL. HRS cells were positive for EBV in 71% (55/77), similar in types I and II. Clonality analysis was performed in 33 cases (type I and type II combined): HRS cells were clonally related to the underlying CLL in 14 and unrelated in 19. ZAP-70 expression of the CLL cells but not EBV status or morphological pattern was correlated with clonal relatedness: all 14 clonally related cases were ZAP-70 negative, whereas 74% (14/19) of clonally unrelated cases were ZAP-70 positive. Overall median survival (types I and II) after diagnosis was 44 months. Advanced age was an adverse risk factor for survival, but not histologic pattern, type I versus type II. HRS-like cells in a background of CLL carries a similar clinical risk to that of CHL-RT and may progress to classic Hodgkin lymphoma in some cases.
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1. Introduction

Approximately 2.2% to 8% (average of 5%) patients with chronic lymphocytic leukemia (CLL) transform into high-grade lymphoma during their clinical course, clinically referred to as Richter syndrome [1,2]. Most cases are diffuse large B-cell lymphoma (DLBCL) [1,3,4]. The classical Hodgkin

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lymphoma (CHL) variant of Richter transformation (CHL-RT) is rare (0.4%-0.7%) [1–3,5–7].

Two different histologic patterns with features of CHL in CLL have been described. Type I is defined as Hodgkin/Reed-Sternberg (HRS) cells scattered in a background of CLL cells, whereas type II has typical CHL morphology showing HRS cells in polymorphous inflammatory background, largely segregated from CLL [8,9]. Although type I morphology has many morphologic and phenotypic features in common with CHL, whether it should be considered as true CHL is still controversial [10,11]. Moreover, few data exist on the implications of a type I diagnosis for patient survival, and cases of type I have been omitted from large retrospective reviews on the subject [6]. Our extensive experience with type I Hodgkin-like lesions based on our consultation practice gave us the opportunity to investigate the type I pattern in greater detail.

HRS cells in most cases of both types I and II have been reported as Epstein-Barr virus (EBV) positive [12]. A correlation between EBV positivity and history of fludarabine treatment was noted, identifying the associated immune suppression as a risk factor [5,6,13,14]. However, EBV-negative cases are not uncommon [1,2,8,15,16]. It remains challenging to draw a conclusion regarding EBV status and its clinical significance in type I and II processes from the small number of cases published in prior reports.

HRS cells can be clonally related to the underlying CLL or may arise as an independent clonal process [8,9,15,17–20]. The association between a clonal relationship and the morphologic pattern has not been studied. Several studies suggested that clonally related HRS cells might be restricted to EBV-negative cases, whereas EBV-positive HRS cells might originate from an unrelated B-cell clone [8,11,18,20]. However, some studies have provided contradictory data arguing against these assumptions [15,17]. What factors determine the clonal relationship between HRS cells and preexisting CLL are still elusive.

We compared 51 cases of CHL-RT with 26 cases of type I Hodgkin-like lesion submitted to our consultation service. Clinical characteristics, morphology, immunophenotype, EBV status, clonality, and overall survival were analyzed.

2. Materials and methods

2.1. Case selection

The pathology database of the Hematopathology Section, Laboratory of Pathology, National Cancer Institute, was searched for cases of CLL accrued since 1990 and reported as containing HRS cells or evidence of CHL. In total, 91 cases were identified. After initial review, 77 cases with 80 biopsies containing cells with the morphology and immunophenotype of HRS cells were included in this study. Among them, 3 cases had 2 sequential biopsies with the first exhibiting type I morphology and the second exhibiting type II; these 3 cases were categorized as type I for further analysis. Fourteen cases were excluded due to insufficient information including EBV status, history of CLL, and follow-up. A history of CLL was determined from pathology reports and patient notes provided by referring physicians. The study was approved by the National Cancer Institute Institutional Review Board. Information on survival was obtained using the National Death Registry identified through DOBsearch.com, if not reflected in patient notes.

2.2. Immunohistochemical staining and in situ hybridization

Sections of formalin-fixed, paraffin-embedded (FFPE) tissue were stained with antibodies against CD30, CD15, Pax5, CD20, EBV LMP1, CD3, CD5, and ZAP-70, using a standard automated technique (Dako or BenchMark XT). EBV in situ hybridization was performed using an EBV-encoded digoxigenin-labeled RNA riboprobe, targeting the EBER RNA transcript of EBV infection as previously described [21].

2.3. Laser capture microdissection

CD30/Pax-5 double-stained, paraffin-embedded sections were used for laser microdissection, using a PixCell IIe laser capture microscope (Acturus Engineering, Santa Clara, CA). A small 7.5-mm spot size with high power at 100 mW and short duration time of 300 microseconds was used for single-cell dissection. Approximately 50 CD30+ HRS cells and 200 Pax5+ CLL cells were dissected and used for direct polymerase chain reaction (PCR) analysis.

2.4. PCR analysis for IGH rearrangement

After microdissection, the thermoplastic membranes containing dissected cells were lifted from laser capture microdissection cap, mixed with Gene Releaser resin (Bioventures, Murfreesboro, TN), preincubated in a Perkin Elmer 480 thermocycler (Applied Biosystems, Foster City, CA), and then used for PCR for IgVH framework III/CDRIII gene rearrangement as previously described [21–23]. The second seminested PCR was performed using 2 μL of 1:100 diluted first PCR product as template with nested JH primer (5′ ACCAGGGTCCCTTGGCCCCA3′) [9] and same VH primer of first-round PCR. The PCR products were then analyzed on 16% polyacrylamide gels and stained with ethidium bromide for visualization [21].

2.5. Statistics

The Student *t* test, Fisher exact test, and log-rank (Mantel-Cox) test were performed using Prism 6 (GraphPad Software, La Jolla, CA). All reported *P* values are 2 sided with a type I error rate of 5% and a $P < .05$ set for significance.

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