World Journal of Surgery and Surgical Research

Case Report
Published: 18 Apr, 2022

Coexistence or Revolution: Clonal Relation between Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma and Composite Lymphoma

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Clinical Practice Points

- Several cases showed occurrence of Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL) and composite lymphoma, while most of the reports could not ascertain that composite one was a primary disease or an evolution of WM/LPL.
- We reported a case that represented the development of a clonal-unrelated diffuse large B-cell lymphoma rather than evolution of the presenting WM/LPL.
- We reviewed 21 cases of WM/LPL which appeared composite lymphoma synchronously or successively, described their clinical-biological characteristics, and highlighted the value of differential diagnosis of clonal relation.

Keywords: Waldenström's Macroglobulinemia/Lymphoplasmacytic lymphoma; Clonal relation; Coexistence; Evolution, Composite lymphoma

Introduction

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL) is a low-grade B-cell lymphoplasmacytic lymphoma [1]. It is characterized with a monoclonal proliferation IgM [2]. WM/LPL showed an indolent clinical course [3], while it can transform to high-grade lymphoma, with an aggressive progression [4]. Several cases showed the concomitant occurrence of WM/LPL and composite lymphoma, being short of data of clonal relation. It is hard to ascertain that composite one is a primary disease or a malignant transformation of WM/LPL. Herein, we reported a case that presented coexistence of WM/LPL and Diffuse Large B-Cell Lymphoma (DLBCL).

Case Presentation

A 61-year-old woman was admitted to hospital because of spinal trauma in 2013. Enlarged lymph nodes and bone destruction were shown. There were no obvious abnormal signs in the brain. Bone marrow smear examination showed that marrow was infiltrated by lymphoplasmacytoid cells. Erythroid cells showed rouleaux formation. Immunohistochemical (IHC) staining of bone marrow biopsy showed a positive result for CD19, CD79α, kappa, CD38. Monoclonal IgM kappa component was confirmed. She was diagnosed with WM/LPL and no treatment was given. In December 2016, she showed a sign of headache and the headache intensified gradually. A cranial Magnetic Resonance Imaging (MRI) scan demonstrated high intensity regions in the right frontotemporal and cerebellar tonsil. Tumor resection was performed in March, 2017. IHC staining of biopsy was positive for CD20, CD79α, Bcl-6 and Ki-67 (80%), and negative for CD38, CD138 (Figure 1A). She was diagnosed with DLBCL. Repeated result of bone marrow smear and biopsy examination was similar to the previous in 2013 (Figure 1B). Concentrations of IgM and serum kappa were significantly high. The biopsy specimens of brain mass and bone marrow were analyzed by Immunoglobulin Heavy chain (IgH) rearrangement. The multiple PCR confirmed that they were from different clonality. The patient received chemotherapy of cyclophosphamide, epirubicin, vindesine, and methylprednisolone, Rituximab (R-CHOP). Methotrexate (MTX) was combined to address the intracerebral lymphoma. After operation and 3 cycles of chemotherapy, there were no new lesions were found. Concentrations of IgM declined gradually, and lymph nodes shrank. The

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Received Date: *23 Jan 2022*
Accepted Date: *01 Apr 2022*
Published Date: *18 Apr 2022*

Citation:
Ma J, Zeng Q, Chen K, Lin Z, Ma Y, Ding T, et al. Coexistence or Revolution: Clonal Relation between Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma and Composite Lymphoma. World J Surg Surgical Res. 2022; 5: 1378.

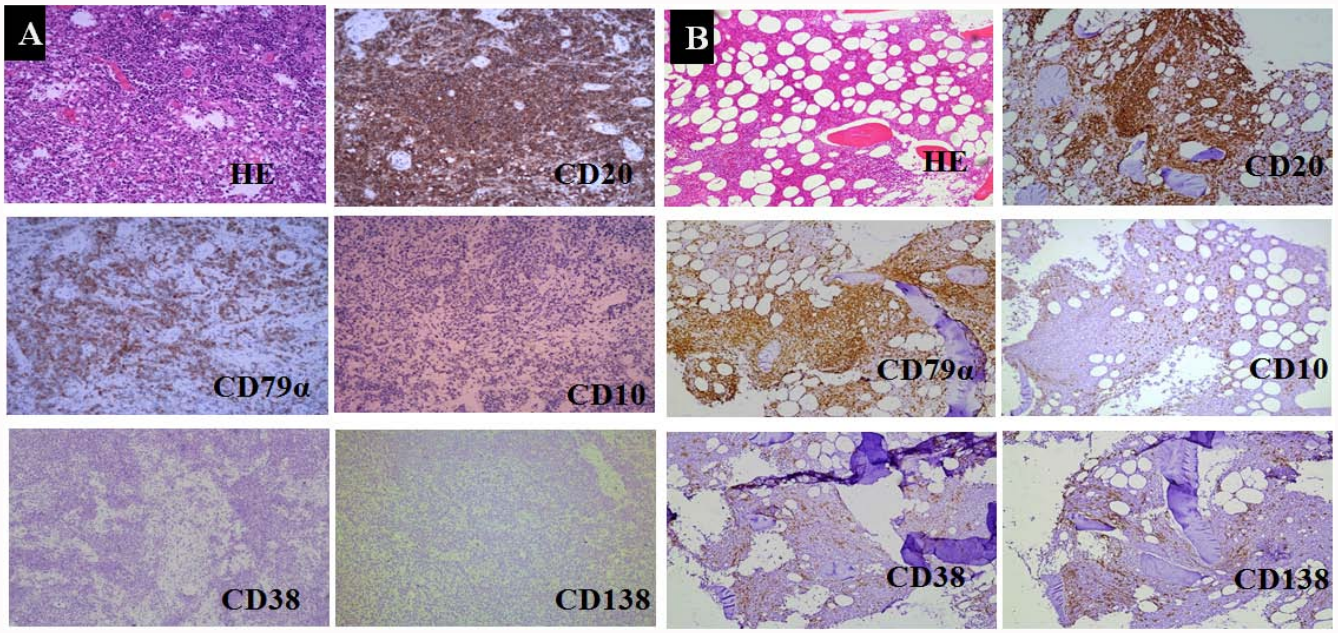

Figure 1A and B: (A) The brain lesion biopsy showed an infiltration of diffused and monomorphic large atypical lymphoid cells. These cells are positive for CD20, CD79α, and negative for CD10, CD38, CD138. (Original magnification: x100). (B) The bone marrow biopsy showed an infiltration of lymphoplasmacytoid cells. These cells are positive for CD20, CD79α, a part of positive result for CD10, CD38, CD138 (original magnification: x100).

Table 1: Clinical characteristics of 21 cases diagnosed with WM/LPL and composite lymphoma.

References	Sex	Age (years)	Interval between WM/LPL and Lymphoma (months)	Lymphoma type*	Involvement site of lymphoma	Treatment of WM/LPL		IgH gene Rearrangement#	Clonal relatedness
						chlorambucil	fludarabine		
[1]	Male	55	204	DLBCL	retroperitoneal mass	no	no	N/A	probable evolution
[4]	Male	73	12	DLBCL	retroperitoneal mass	N/A	N/A	N/A	probable evolution
[5]	Male	53	72	IL	lymph node	no	no	N/A	probable evolution
[5]	Male	69	144	IL	supraclavicular mass	yes	no	N/A	probable evolution
[6]	Male	60	36	DLBCL	subcutaneous nodule	no	no	N/A	probable concomitant
[7]	Male	75	10	DLBCL	skin lesion	no	yes	N/A	probable evolution
[8]	Female	56	36	PTCL	lymph node	no	yes	N/A	unsure
[8]	Male	65	84	DLBCL	lymph node	yes	no	N/A	probable concomitant
[10]	Male	57	120	IL	lymph node	yes	no	N/A	probable evolution
[15]	Male	66	36	DLBCL	lymph node	no	no	monoclonality	evolution
[17]	Male	75	12	DLBCL	brain mass	no	no	different clonality	concomitant
[18]	Female	70	108	BL	neck mass	no	yes	monoclonality	evolution
[19]	Female	73	0	DLBCL	brain mass	no	no	N/A	unsure
[20]	Male	46	216	EMZL	brain mass	no	no	monoclonality	evolution
[21]	Male	80	36	DLBCL	mesenteric mass	yes	yes	N/A	probable concomitant
[22]	Female	72	0	MALT	kidney mass	no	no	N/A	probable evolution
[23]	male	59	0	MALT	gastric fundus	yes	no	N/A	unsure
[24]	Male	69	10	DLBCL	adrenal mass	no	no	different clonality	concomitant
[25]	Male	76	36	MALT	ocular mass	no	no	N/A	probable concomitant
[26]	Male	59	36	ALCL	lymph node	no	no	N/A	unsure
Our case	Female	61	36	DLBCL	brain mass	no	no	different clonality	concomitant

*DLBCL: Diffuse Large B-Cell Lymphoma; MALT: Mucosa-Associated Lymphoid Tissue Lymphoma; IL: Immunoblastic Lymphoma; PTCL: Peripheral T-Cell Lymphoma; EMZL: Extranodal Marginal Zone Lymphoma; BL: Burkitt Lymphoma; ALCL: Anaplastic Large Cell Lymphoma

#N/A: Not applicable

patient is still under follow-up.

Discussion

For a patient diagnosed with WM/LPL, the emerging lymphoma can develop by clonal evolution from WM/LPL or occur as a secondary neoplasm. The clinical-biological characteristics of the two diseases were not well-known [5]. Herein we reviewed 21 cases of WM/LPL, which were diagnosed with composite lymphoma synchronously (3 cases) or successively (18 cases). It's found that male patients are more than female patients. The median age of diagnosing with WM/LPL was 66 years old and the median interval time between diagnosing with WM/LPL and composite lymphomas were 36 months (Table 1). The most common types of composite lymphoma were DLBCL, Mucosa-Associated Lymphoid Tissue lymphoma (MALT), and Immunoblastic Lymphoma (IL).

Concerning pathogenesis of evolution or coexistence, Richter's syndrome occurred in 6% of patients with WM/LPL [6]. Some patients were diagnosed with DLBCL after treated with nucleoside analogues [7,8]. In our review, 14 patients were given therapy after diagnosing with WM/LPL and 64.3% of them were treated with chlorambucil or fludarabine, or both drugs (Table 1). Lin et al. had analyzed 10 cases of transformation while failed to demonstrate the evidence of Epstein Barr Virus (EBV) [9]. In our review, most of the cases were lack of the detection result of EBV, so the overall incidence of EBV-associated lymphoma is unclear.

To judge clonal relation the presence of surface immunoglobulin was not sufficient [9-10]. Some reports suggested that neoplastic clone of WM/LPL would reduce of the ability to secrete IgM and represent the fall in serum IgM concentration during the appearance of high-grade lymphoma [11]. Some reports suggested genetic analysis should be examined [12-13]. The Complementarity-Determining Region 3(CDR3) in the IgH gene of each lymphocyte is unique, so analysis of IgH gene especially CDR3 could be used to identify the clonality [14]. In our case, we confirmed the clonal relation by rearrangement of IgH. In our review, specimens were examined of clonal rearrangement of IgH in 6 cases. Probable coexistence or evolutions were considered based on the clinical character and light chain restriction in 11 cases (Table 1). There was no established treatment regimen, and rituximab may improve the treatment outcome [15]. It's speculated that clonally unrelated cases showed poorer prognosis than related cases [16-17].

Conclusion

Clonal relation between WM/LPL and composite lymphoma is in dispute. We reviewed 21 cases and highlighted the pathogenesis and methods for differentiation, especially the role of genetic analysis. The number of analyzed cases is too small to clarify outcome and it is necessary to accumulate more clinic studies.

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