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Original Article

MUM-1 expression differentiates AITL with HRS-like cells from cHL

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Abstract: MUM1 is a member of the interferon regulatory factor family of transcription factors. It is normally expressed in plasma cells, late B cells, and activated T cells, and has been described in several B-cell malignancies and some T-cell neoplasms. The aim of our study was to evaluate the role of MUM-1/IRF4 protein in differentiating angioimmunoblastic T cell lymphoma (AITL) with Hodgkin/Reed-Sternberg (HRS)-like cells from cHL. We identified 12 cases of AITL with HRS-like cells and 24 cases of cHL from March 2013 to November 2014. IHC for MUM-1/IRF4 protein was performed on the tissue of these cases and some relevant positive and negative controls. MUM-1 was expressed in HRS-like cells and some neoplastic T-cells in AITL with HRS-like cells (12/12, 100%) and formed the rosettes around the HRS-like cells (12/12, 100%), expressed in HRS cells in classic Hodgkin Lymphoma (cHL) (24/24, 100%) and just one case formed rosettes around the HRS cells (1/24, 4.2%). Based on the results, MUM-1 could be a useful marker for the differential diagnosis between AITL with HRS-like cells and cHL.

Keywords: MUM-1, AITL with HRS-like cells, cHL, differential diagnosis, immunohistochemistry

Introduction

Angioimmunoblastic T cell lymphoma (AITL) with Hodgkin/Reed-Sternberg (HRS)-like cells is a special peripheral T cell lymphoma, which derived from follicular T helper cells and has been reported just a few cases in the worldwide in the past. Recent years, much attention has focused on the HRS-like cells [1, 2]. Not only the HRS-like cells have similar morphological feature with HRS cells, but also the immunophenotypes of them are approximatively. The challenge question is the differential diagnosis between AITL with HRS-like cells and cHL. Since they have different therapeutic methods and prognosis, differentiating for them are very important. Our data showed that 5 of 12 cases of AITLs with HRS-like cells were initially diagnosed as cHL and treated for cHL. Owing to poor treatment effect, the patients consulted to our institution and diagnosed to AITL with HRS-like cells eventually.

It seems that we have some difficulty to distinguish them, for the HRS-like cells and HRS cells have similar morphology and immunophenotype. Interestingly, in our study, we found that the immunophenotype of MUM1 was different in AITL with HRS-like cells and classical Hodgkin's lymphoma.

Multiple myeloma (MM) antigen 1 (MUM1) is normally expressed in plasma cells, melanocytes, some B cells, and activated T cells [3]. Studies showed that MUM1 protein is required at several stages of B-cell development, including in the differentiation of mature B cell into antibody-secreting plasma cells [4], and is also critical for Th2 and Th17 T-cell differentiation [5] and T-cell cytotoxic function [6].

Immunohistochemistry (IHC) for MUM1 has been widely used to support the diagnosis of lymphomas such as cHL, ALCL and plasma cell tumors. Besides, MUM1 was reported for the diagnosis of cHL with high sensitivity and speci-

Table 1. Primary antibodies and conditions used for immunohistochemical staining

Antigen	Clone	Dilution	Antigen retrieval	Source
CD20	L26	1:200	HP EDTA	Maixin.Bio
CD3	SP7	1:100	HP EDTA	Maixin.Bio
CD21	EP3093	1:50	HP EDTA	Maixin.Bio
CD30	Ber-H2	1:20	HP EDTA	Maixin.Bio
CD15	Carb-3	1:20	HP EDTA	Maixin.Bio
CD10	56C6	Ready to use	HP EDTA	Maixin.Bio
BCL-6	LN22	1:20	HP EDTA	Maixin.Bio
PD-1	NAT	1:40	HP EDTA	Maixin.Bio
CXCL-13	Polyclone	1:100	HP EDTA	Maixin.Bio
PAX-5	SP34	1:50	HP EDTA	Maixin.Bio
MUM1	MUM1p	1:50	HP EDTA	Maixin.Bio
Ki-67	MIB-1	1:200	HP EDTA	Maixin.Bio

HP EDTA: Boiling with EDTA (1 mM pH 9.0) under high pressure.

ficity and expressed in almost all cases of cHL [7, 8].

However, the value of MUM1 for the differential diagnosis in AITL with HRS-like cells and cHL has never been mentioned in the past. In this study, we try to evaluate the role of MUM-1/IRF4 protein in differentiating AITL with HRS-like cells from cHL.

Methods

Cases

12 cases of angioimmunoblastic T cell lymphoma with HRS-like cells and 24 cases of cHL were obtained retrospectively from the files of the Department of Pathology, Beijing Friendship Hospital, Capital Medical University, (Lymphoma Diagnostic Center, Beijing Clinical Medical Institute) a large lymphoma diagnosis research center, located in Beijing China. All cases were received for consultation in the hospital between March 1, 2013 and November 31, 2014. Hematoxylin and eosin stained (H&E) and immunohistochemistry were available for study for all cases. Some necessary immunostaining and molecular studies were further performed for differentiated diagnosis. A diagnostic criterion was based on established according to the 2008 World Health Organization classification of Tumors of Haematopoietic and Lymphoid Tissues.

Immunohistochemistry

The MaxVision^{TM2} kit provided by Maxin Bio (Cat.No.KIT-5910/5931) was used for detection of all antigens. The pretreatment methods, primary antibodies and their working dilutions used in this study are listed in **Table 1**.

In situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER)

The EBV Probe In Situ Hybridization Kit (TRIPLEX INTERNATIONAL BIOSCIENCES, CHINA, CO. LTD) was used to detect EBERs according to the following steps: (1) deparaffinization and dehydration of the paraffin sections using xylene and a series of graded ethanol; (2) pretreatment with proteinase K for 5 minutes; (3) hybridization with digoxigenin-conjugated EBV (EBERs) probe at 37°C for 4 hours; (4) signal detection using peroxidase-conjugated anti-digoxigenin antibody and 3,3'-diaminobenzidine (DAB); and (5) counterstaining the sections with hematoxylin solution. The positive signals were brownish-yellow and localized within the nuclei.

Molecular studies

Studies of T-cell receptor β and δ chain were available in 5 cases. BIOMED-2 polymerase chain reaction (PCR) was carried out on whole tissue extracts from paraffin-embedded tissue. The PCR reactions were run according to the following steps: (1) DNA was extracted from paraffin-embedded tissue after dewaxing by using the TIANamp FFPE DNA Kit (TIANGEN, DP331); (2) Detecting the concentration and purity of DNA by using ultramicro spectrophotometer of the Thermo Scientific company, US; (3) Verifying the quality of the extracted DNA by Specimen control size ladder mix of Identi Clone^{TM} TCR Gene Clonality Assay, Invivo Scribe. The PCR products were seen as qualified DNA when above 300 bp and disqualification when under 300 bp. (4) The qualified DNA was used to analyze for gene rearrangement and all the experiments included monoclonal, polyclonal, and blank control groups.

Results

Pathologic findings

All 12 cases of AITL with HRS-like cells showed two kinds of growth patterns: 9 cases showed nodular growth pattern and other 3 cases were diffuse growth pattern. The HRS-like cells had abundant pale cytoplasm and uni-, bi or multilo-

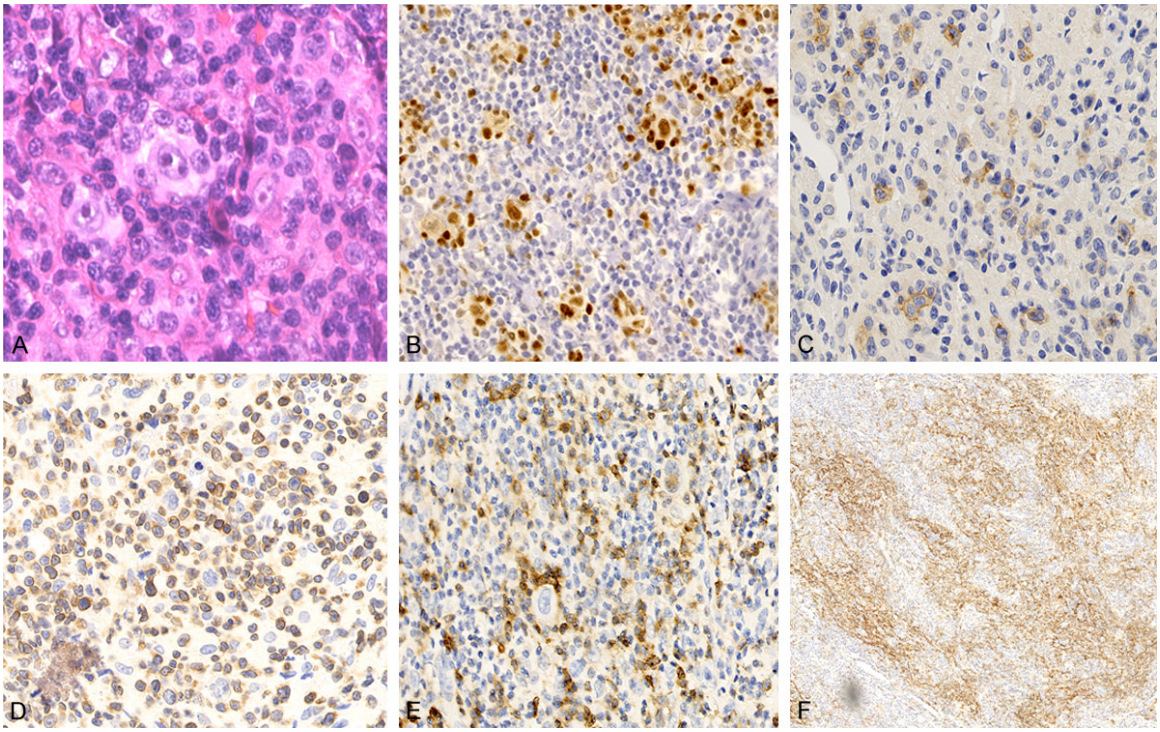

Figure 1. AITL with HRS-like cells. A. H&E-stained sections, The HRS-like cells had abundant pale cytoplasm and uni-lobated nuclei with prominent eosinophilic nucleoli. B. MUM1 immunostain highlighting the rosettes around the HRS-like cells. C. CD30 was positive for HRS-like cells. D. CD3 immunostain. E. CD10 immunostain showing positive staining of neoplastic T cells. F. CD21 showing expanded and irregular follicular dendritic cell network.

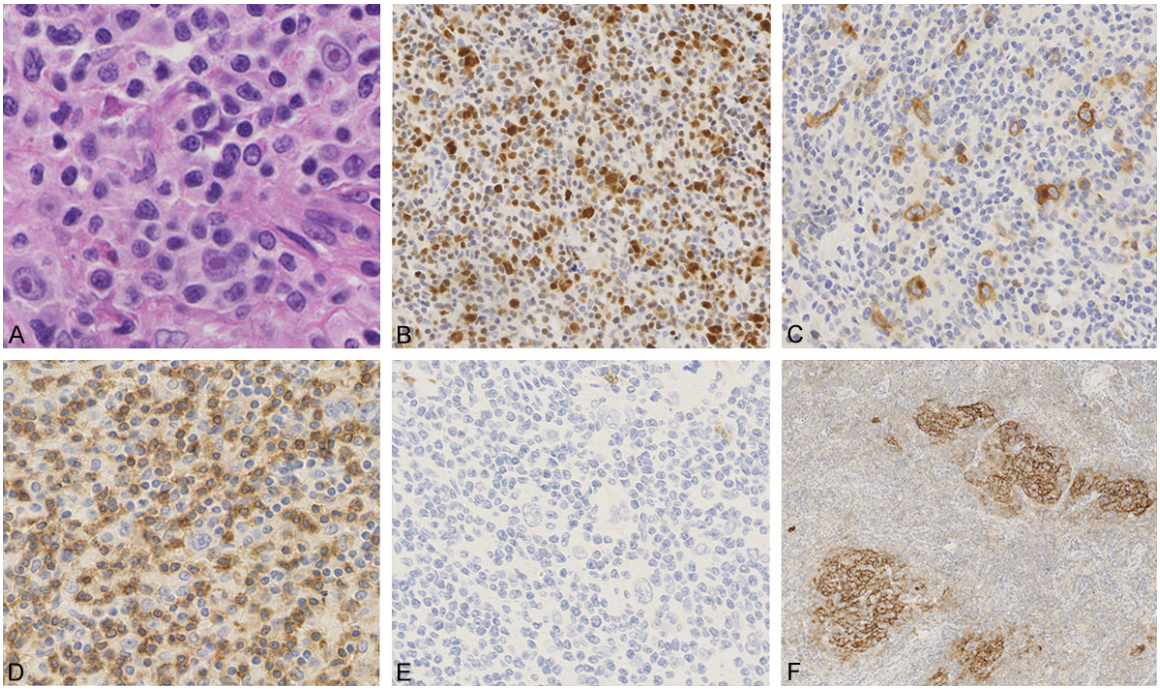

Figure 2. Classical Hodgkin Lymphoma. A. H&E-stained sections, presented with mononuclear HRS cells. B. RS cells with nuclear positivity for MUM1 but no rosettes around the HRS-like cells. C. CD30 was positive for HRS cells. D. CD3 immunostain. E. CD10 immunostain showing negative staining of background T cells. F. CD21 showing lack of expanded and irregular follicular dendritic cell network.

Table 2. MUM1 protein expression in paraffin section of AITL with HRS-like cells and cHL

Lymphoma type	MUM1 expression
AITL with HRS-like cells	
HRS-like cells	12/12 (100%)
Neoplastic T-cells	12/12 (100%)
Classical hodgkin lymphoma	
HRS cells	24/24 (100%)
The background T cells	1/24 (4.2%)

bated nuclei with prominent eosinophilic nucleoli (**Figure 1A**) which mimics the HRS cells of cHL (**Figure 2A**). 10 cases showed the atypical neoplastic T cells were medium sized lymphocytes with round to angulated nuclei and abundant pale cytoplasm, and clustered distribution in the background of the lesion. In cHL, all 24 cases showed nodular growth pattern. The background of cHL contained small lymphocytes, histiocytes, plasma cells, eosinophils and rare polymorphonuclear leukocytes but no atypical neoplastic cells with pale cytoplasm distributed in the background of the lesion.

Immunophenotypic findings

The immunophenotype of MUM1 in both AITL with HRS-like cells and cHL are summarized in **Table 2**. In all 12 cases of AITL with HRS-cells, MUM1 expessed in both HRS-like cells and some neoplastic T-cells forming the rosettes around the HRS-like cells (**Figure 1B**). CD30 (**Figure 1C**) was positive for HRS-like cells in all cases, only one case was positive for CD15 in 9 available cases. PAX5 was variable intensity and 4 of them showed weakly positivity in all available 6 cases. The atypical T lymphoid cells in all cases of AITL with HRS-like cells had a TFH immunophenotype and they were positive for CD3 (**Figure 1D**), CD10 (**Figure 1E**), Bcl-6, PD-1, and CXCL-13. Besides, CD21 showed expanded and irregular follicular dendritic cells (FDC) net (**Figure 1F**).

For all 24 cases of cHL, HRS cells were positive for MUM1 (**Figure 2B**), but just one case showed rosettes around the HRS cells. CD30 (**Figure 2C**) was positive for HRS cells in all cases, half of the cases were positive for CD15. PAX5 was variable intensity and 23 cases showed weakly positivity in all cases. The background T cells were positive for CD3 (**Figure 2D**) but negative for CD10 (**Figure 2E**), CD21 showed the unexpanded and regular FDC net (**Figure 2F**).

In situ hybridization

Eight cases showed HRS-like cells were positive for EBER ISH in all cases of AITL with HRS-like cells (8/12) and five cases stained positive in cHL (5/19).

Molecular findings

Five cases showed clonal TCR rearrangement in all available fives cases of AITL with HRS-like cells (5/5).

Discussion

Angioimmunoblastic T cell lymphoma (AITL) with Hodgkin/Reed-Sternberg (HRS)-like cells is a rare peripheral T cell lymphoma and proliferation of HRS-like cells in AITL occurred as a result of immune suppression and were generally regarded as the Epstein-Barr virus (EBV)-infected B-cells with morphological features similarities to classical Reed-Sternberg cells. Pathologists usually misdiagnose AITL with HRS-like cells as cHL. As a matter of fact, 5 of our cases had been misdiagnosed to cHL before the consultation.

Distinguishing cHL from AITL with HRS-like cells is critical and important, since they have totally different therapeutic regimens and prognosis. However, it is usually not very easy to distinguish them. Though the clustered neoplastic T cells with pale cytoplasm in some cases of AITL with HRS-like cells can help to the differencial diagnosis, not all the cases could apparently display such classic T cells. Clinical history such as fever, weight lose or night sweat, even ascites may seem to be in favor of in AITL with HRS cells, but few cases still showed similar clinical histories to cHL. Besides, though microdissection studies indicated that the HRS-like cells in AITL represent oligoclonal and not monoclonal B-cell populations [9] which are different from the HRS cells of cHL. But microdissection method wouldn't be convenient for our daily works. So trying to find a useful way to differentiate these two diseases is necessary.

Morphologigally, our 12 cases of AITL with HRS-like cells showed 9 cases of nodular growth pattern and 3 cases of diffuse growth pattern, while all 24 cases of cHL displayed nodular

growth pattern. The HRS-like cells had abundant pale cytoplasm and uni-, bi or multilobated nuclei with prominent eosinophilic nucleoli, which were mimic the RS cells of cHL. 10 cases of AITL showed the atypical neoplastic T cells were medium sized lymphocytes with round to angulated nuclei and abundant pale cytoplasm, and clustered distribution in the background of the lesion, but no cases of cHL showed atypical T neoplastic cells with pale cytoplasm distributed in the background of the lesion. However, the challenge question is that few cases of AITL with HRS-like cells are difficult to differentiate with cHL when the morphologies are not so typically.

In immunophenotypes, the HRS-like cells had similar traits with classic Hodgkin cells [10]. Our study basically showed the same results: all 12 cases of AITL with HRS-like cells showed strong membrane staining for CD30, only one case was positive for CD15. Most of the cases expressed CD20 (6/9), PAX5 was positive in all available cases (variable intensity, 6/6). In cHL, CD30 expressed in all cases, and PAX5 expressed in almost all cases (23/24). However, we found that there were different immunophenotypical characteristics between them: the staining of HRS-like cells and neoplastic T-cells were positive for MUM1 and formed the rosettes around the HRS-like cells in all 12 cases of AITL with HRS-like cells (12/12), but only one case showed rosettes around the HRS cells in 24 cases of cHL (1/24). To the best of our knowledge, no study has previously reported on the special immunoreactivity. Our finding revealed that 100% of cases of AITL with HRS-like cells formed rosettes comparing to only 4.2% of cases of cHL. This finding may serve as a useful discriminator for the two cases. It may also be a particularly helpful tool when cases exhibit morphologic and/or immunohistochemical overlap with cHL.

The reasons about MUM1 displaying the rosettes in AITL with HRS-like cells were still not very clear,one hypothesis for this phenomenon is that MUM1 is expressed not only in HRS-like cells but also in the neoplastic T-cells around the HRS-like cells. Alina Nicolae [1] believed that rosetting by the neoplastic T-cells derived from follicular T helper (TFH) in these lymphomas might be protecting aberrant B cell clones from immune surveillance, leading to the emergence of HRS-like cells we observed. Immunodeficiency could be an essential factor for the occurrence of such phenomenon, and it has generally been assumed that the HRS-like cells expanded due to defects in immune surveillance [11].

MUM1/IRF4 protein expressed in HRS cell in almost all cases of cHL [12-14], however, only one case showed rosettes in our datas. The most possible reason for such phenomenon we inferred is that the inflammatory cells around the HRS cell were activated T cells, which were positive for MUM1.

The origin of HRS cells has been enigmatic for a long time, as they often express markers of different hematopoietic lineages [15]. Only recently the analyses of immunoglobulin and T-cell receptor loci of single HRS cells revealed that they represent monoclonal populations of tumor cells of B-cell (98%) or T-cell (2%) origin [16, 17]. In most instances cHL is a B-cell lymphoma, H/RS cells are derived from germinal center (GC) or post-GC B-cells, they harbor clonally rearranged immunoglobulin genes and carry a high load of somatic mutations [18]. MUM1/IRF4 is expressed in the final step of intra-GC B-cell differentiation, in subsequent steps of B cell maturation towards plasma cells, in lymphoid neoplasms thought to be derived from these cells and in activated T cells. Due to activating T cells around the HRS cell is a rare event in cHL, so we can hardly see rosettes in cHL.

In addition to distinguishing cHL from AITL with HRS-like cells, the differenciate diagnosis of composite lymphoma could be another challenge question. Such lymphoma was usually thought to arise from two different clones, occasional cases may be related clonally and represent progressively evolutionary stages of the same neoplastic clone [19-21]. The occurrence of a composite lymphoma involving both T and B-cell lineages is an unusual event and just a few cases have been reported in the literature [22-25]. Microdissection studies have showed that the HRS-like cells represent oligoclonal and not monoclonal B-cell populations [9], and our molecular study showed that five cases were clonal TCR rearrangement in all available fives cases of AITL with HRS-like cells, which excluded the possibility of classical Hodgkin lymphoma. Besides, MUM1 may be useful for the differenciate diagnosis: MUM1

would display the special rosettes around the HRS-like cells but not for the HRS cells in a composite lymphoma, which is different from the AITL with HRS-like cells.

Conclusions

In summary, our results show that MUM1 expressed in HRS-like cells and neoplastic T-cells derived from follicular T helper (TFH) of AITL with HRS-like cells and formed rosettes around the HRS-like cells. Though MUM1 was expressed in HRS cells of cHL, we can hardly find the rosettes around the HRS cells. This phenomenon suggests that MUM1 may be a helpful marker in the differential diagnosis of AITL with HRS-like cells and cHL, however, further studies on this topic with a larger number of cases is neccessary.

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Disclosure of conflict of interest

None.

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