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Clinical analysis of 20 patients with non-Hodgkin lymphoma and autoimmune hemolytic anemia

A retrospective study

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Abstract

Non-Hodgkin lymphoma (NHL) can co-exist with autoimmune hemolytic anemia (AIHA), a phenomenon known as AIHA-associated NHL (AIHA/NHL). However, few studies have reported AIHA/NHL incidence or its clinical characteristics. We conducted a retrospective analysis of 20 AIHA/NHL patients treated at our hospital from 2009 to 2018. AIHA/NHL was presented by only 0.91% of the NHL and 9.8% of the AIHA patients. In addition, AIHA occurred most frequently with angioimmunoblastic T-cell lymphoma (AITL) (7.31%), followed by marginal zone B-cell lymphoma (MZBL) (6.25%), B-cell lymphoma-unclassified (BCL-U) (4.25%), chronic lymphocytic leukemia/small lymphocyte lymphoma (CLL/SLL) (2.50%), and mantle cell lymphoma (MCL) (2.30%). In addition to the CLL/SLL patients with impaired bone marrow, 66.7% of the AIHA/NHL patients had lymphoma bone marrow infiltration (LBMI), of which 4 patients presented LBMI in bone marrow smears (BMS) but not in bone marrow biopsy (BMB) and 6 were positive for BMB but not BMS. The 1-, 3- and 5-year survival rates of AIHA/NHL patients were 70%, 30% and 20%, respectively, and they responded poorly to chemotherapy. In conclusion, AIHA can co-exist with various NHLs and the defining clinical characteristic of AIHA/NHL is the high incidence of LBMI. However, both BMS and BMB should be performed to avoid missed diagnosis.

Abbreviations: AIHA = autoimmune hemolytic anemia, AIHA/NHL = AIHA associated NHL, AITL = angioimmunoblastic T-cell lymphoma, BCL-U = B-cell lymphoma-unclassified, BMB = bone marrow biopsy, BMS = bone marrow smears, CLL/SLL = chronic lymphocytic leukemia/small lymphocyte lymphoma, CR = complete remission, LBMI = lymphoma bone marrow infiltration, MCL = mantle cell lymphoma, MZBL = marginal zone B-cell lymphoma, NHL = non-Hodgkin's lymphoma, PR = partial remission.

Keywords: autoimmune hemolytic anemia, diagnosis, lymphoma bone marrow infiltration, non-Hodgkin lymphoma, treatment

1. Introduction

Autoimmune hemolytic anemia (AIHA) is caused by hyperfunctioning B lymphocytes, which produce large amounts of autoantibodies and/or complement that are adsorbed on red blood cells (RBCs), resulting in their rapid lysis following antigen-antibody reaction. Primary AIHA does not have any underlying diseases, whereas secondary AIHA accompanies immune-related and lymphatic proliferation diseases, measles, EB and cytomegalovirus infections, as well as leukemia, thymoma, and colon cancer.[1–4]

Lymphomas are solid hematological tumors that originate in lymph nodes or lymphoid tissues, and are classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), depending on the presence or absence of Reed–Sternberg cells. NHLs include diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue lymphoma, marginal zone B-cell lymphoma (MZBL), peripheral T-cell lymphoma (PTCL), etc.[5,6]. The etiology and pathogenesis of lymphoma are still unclear, although viral infections, oncogenic mutations, radiation and chemical exposure, and autoimmune diseases have been variously implicated.[7–10]

Roughly one-fifth of AIHA patients develop lymphoma, while 7% to 10% of lymphoma patients have co-existing AIHA, indicating a clinicopathological link between both diseases.[2,3,11,12] The incidence of AIHA/NHL is relatively rare,[3] and few reports are available regarding its clinical characteristics. To this end, we conducted a retrospective study of 20 cases of AIHA/NHL that were diagnosed at our hospital in the last 10 years.

2. Materials and methods

Clinical and laboratory data of the AIHA/NHL patients that were treated at our hospital from January 2009 to December 2018 were retrospectively analyzed. AIHA was diagnosed on the basis of anemia, elevated reticulocyte count, high levels indirect bilirubin, and positive direct antihuman globulin test. Since

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AIHA usually precedes or occurs during the complete remission (CR) of NHL, patients initially diagnosed with AIHA without any signs of NHL were treated as per the AIHA treatment guidelines.[9,13] In contrast, patients presenting first with NHL with or without accompanying AIHA were treated as per the NCCN treatment guidelines for NHL.[14,15]

NHL was confirmed in all patients of our cohort by bone marrow smears (BMS), bone marrow biopsy (BMB) or lymph node biopsy. In addition, immune-phenotyping was performed for the T cell markers CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD45RO, Cxcl-13, TIA-1, and ALK, B cell markers including CD10, CD19, CD20, CD21, CD79, Pax5, Bcl-2 and Bcl-6, and the NK cell marker CD56. The NHL stage was determined by routine blood tests, liver and kidney function tests, chest CT, and abdominal B-ultrasound. The classification of NHL was based on the WHO 2008 and 2016 lymphoma classification criteria,[16,17] and further staging and subgrouping were based on the Ann Arbor criterion (the staging of CLL/SLL was based on the Rai criterion).

The efficacy of NHL treatment was evaluated after 4 courses of chemotherapy. In case a patient simultaneously presented with AIHA, the efficacy of AIHA treatment was also evaluated. If CR of NHL was obtained, the original chemotherapy regimens would be used to consolidate the chemotherapy 2 courses and ended the treatment. If CR of NHL was not obtained, the efficacy would be re-evaluated after 2 courses of chemotherapy with the original chemotherapy regimens. If CR was obtained, the original chemotherapy regimens would be used to consolidate the chemotherapy 2 courses to end the chemotherapy. Otherwise, radiotherapy or hematopoietic stem cell transplantation would be used.

2.1. Ethics statement

Written informed consents were obtained from all the parents of the patients and their donors in accordance with the Declaration of Helsinki. And it was approved by the ethics committee of the first affiliated hospital of Guangxi Medical University, Guangxi, China.

3. Results

At total of 2204 NHL and 204 AIHA patients admitted to our hospital in the period between January 2009 and December 2018, of which 20 patients were diagnosed with AIHA/NHL and accounted for 0.91% and 9.8% of the NHL and AIHA cases, respectively. The clinical characteristics of 20 AIHA/NHL patients are summarized in Table 1. There were 14 males and 6 females in our cohort, with ages ranging from 39 to 85 years and median age 60 years. All patients were at stage III to IV of NHL, and the distribution is shown in Table 2. The incidence of AIHA was highest in patients with angioimmunoblastic T-cell lymphoma (AITL) (7.31%), followed by MZBL (6.25%), BCL-U (4.25%), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (2.50%) and mantle cell lymphoma (MCL) (2.30%). The B-cell lymphoma diagnosed in 47 of the 2204 NHL patients could not be classified further, and the patients were thus grouped under BCL-U. In addition, since CLL and SLL have similar characteristics, patients with either were grouped together as SLL/CLL.

The laboratory characteristics of the AIHA/NHL patients are summarized in Table 3. Nineteen patients harbored warm-reactive autoantibodies whereas 1 had cold-reactive autoantibodies. In addition, 6 patients each had high levels of C3 or IgG in the sera, and 8 were positive for C3 and IgG. AIHA was diagnosed 0 to 6656 days before NHL diagnosis in 12 patients, and 1 to 2121 days after NHL diagnosis in 8 patients. Among the 5 CLL/SLL cases, patients 9 and 16 were simultaneously diagnosed with AIHA and lymphoma, and patients 18, 19, and 20 were diagnosed with CLL/SLL, respectively, 225, 1619, and 2121 days before AIHA. All patients underwent BMS and BMB, and 10 also underwent lymph node biopsy. In addition to the CLL/SLL patients, 10 others showed lymphoma bone marrow infiltration (LBMI), resulting in a high 66.7% overall incidence in the AIHA/NHL cohort. Among the non-CLL/SLL patients with LBMI, BMS was positive and BMB was negative in 4 cases, including 2 of DLBCL, and 1 each of PTCL and MZBL. In addition, BMB was positive and BMS was negative for LBMI in 6 cases, including 2 of MCL, and 1 each of MZBL, FL, AITL and BCL-U.

During AIHA treatment, patients 1 to 6 (see Table 4) were treated with prednisone alone, and the remaining received glucocorticoid and combined chemotherapy for NHL. Patients 1,

Table 1

Summary of the characteristics of 20 patients with AIHA/NHL.

Points	n	%
Age, yrs		
Median	60	–
Range	39–85	–
Sex		
Male	14	70.00
Female	6	30.00
Stage of NHL		
III	3	15.00
IV	17	85.00
AIHA		
Warm, C3	6	30.00
Warm, IgG	6	30.00
Warm, C3+IgG	7	35.00
Cold, C3	1	5.00

AIHA = autoimmune hemolytic anemia, NHL = non-Hodgkin lymphoma.

Table 2

Distribution in NHL subtypes of 20 patients with AIHA/NHL.

Subtypes	n	AIHA/NHL	%
NHL	2204	20	0.91
CLL/SLL	200	5	2.50
DLBCL	904	3	0.33
AITL	41	3	7.32
MCL	87	2	2.30
BCL-U	47	2	4.25
MZBL	32	2	6.25
ALCL	94	1	1.06
FL	87	1	1.15
PTCL	81	1	1.23

AIHA = autoimmune hemolytic anemia, AITL = angioimmunoblastic T-cell lymphoma, ALCL = anaplastic large cell lymphoma, BCL-U = B cell lymphoma (classification unknown), CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma, DLBCL = diffuse large B cell lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma, MZBL = marginal zone B-cell lymphoma, NHL = non-Hodgkin Lymphoma, PTCL = peripheral T-cell lymphoma.

Table 3

The laboratory characteristics of 20 patients with AIHA/NHL.

NUM	Age/sex	Lymphoma	AIHA	BMS	Bispy 1	Bispy 2	Time, d
1	58/M	PTCL, IVB	W, IgG	+	−	+	+6656
2	71/M	DLBCL, IVA	W, IgG	+	−	+	+4332
3	50/F	ALCL, IIIA	W, C3+IgG	−	−	+	+783
4	61/M	MCL, IVB	C, C3	−	+	NA	+65
5	76/F	AITL, IVB	W, C3+IgG	−	−	+	+58
6	55/M	MZBL, IVA	W, C3	−	+	+	+45
7	45/M	DLBCL, IVB	W, C3	−	−	+	+24
8	59/F	MZBL, IVB	W, IgG	+	−	NA	+18
9	81/F	SLL, IV	W, C3	+	+	NA	+13
10	85/M	BCL-U, IVB	W, C3+IgG	−	+	NA	+13
11	39/M	MCL, IVA	W, C3+IgG	−	+	NA	+11
12	47/M	DLBCL, IVB	W, C3	+	−	+	0
13	58/M	FL, IVA	W, IgG	−	+	NA	−1
14	52/M	AITL, IVB	W, C3+IgG	−	+	+	−3
15	72/F	BCL-U, IVB	W, C3+IgG	NA	NA	NA	−4
16	76/M	CLL, III	W, C3+IgG	+	−	NA	−7
17	66/F	AITL, IVB	W, IgG	−	−	+	−10
18	62/M	CLL, III	W, C3	+	+	NA	−225
19	65/M	SLL, IV	W, IgG	+	+	+	−1619
20	54/M	CLL/SLL, IV IVB	W, C3+IgG	+	+	NA	−2121

AIHA = autoimmune hemolytic anemia, AITL = angioimmunoblastic T-cell lymphoma, ALCL = anaplastic large cell lymphoma, BCL-U = B cell lymphoma (classification unknown), Bispy1 = bone marrow bispy, Bispy2 = lymph node Bispy, BMS/Bispy1/Bispy2 = "+" means Positive, "−" means Negative, and "N" means no examination, BMS = bone marrow smear, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B cell lymphoma, MCL = mantle cell lymphoma, MZBL = marginal zone B-cell lymphoma, NA = not available, NHL = non-Hodgkin lymphoma, PTCL = peripheral T-cell lymphoma, SLL = small lymphocyte lymphoma, Time = the time between diagnosis AIHA and diagnosis lymphoma, "+" means diagnosis AIHA first, and "−" means diagnosis lymphoma first.

2, 8, 13, and 19 achieved CR, and the others showed partial remission (PR) or no remission (NR). Patients 8, 9, 12, 13, 18, 19, and 20 received 4 or more courses of combined chemotherapy, of which only patients 8 and 9 achieved CR. In the follow-up to January 2019, 7 of the 20 patients were still alive. The 1-, 3- and 5-year survival rates were 70%, 30% and 20%, respectively. Among the 4 patients that survived for >5 years, NHL occurred in patients 1 and 2 after 18 and 11 years of AIHA,

Table 4

Treatment and results of AIHA/NHL patients.

NUM	Treatment 1	Results 1	Treatment 2	Results 2	Status	Survival time, month
1	Pred	CR	2EPOCH	–	Died	224.0
2	Pred	CR	3RCHOP	–	Survived	168.0
3	Pred	PR	EPOCH	–	Died	31.1
4	Pred	PR	3EPOCH	–	Survived	29.4
5	Pred	NR	3RCOP	–	Died	38.6
6	Pred	PR	–	–	Died	17.3
7	Pred	NR	1Hyper CVAD+R	–	Died	5.3
8	Pred	CR	6RCHOP	CR	Survived	36.9
9	Pred	PR	6RCOP+2RFC+1RFD	CR	Died	35.5
10	Dxm	NR	–	–	Died	3.2
11	Dxm	NR	2REPOCH	–	Survived	1.4
12	Dxm	NR	4RCHOP	NR	Died	4.7
13	–	CR	6RCHOP	PR	Survived	31.4
14	–	NR	EPOCH	–	Survived	28.4
15	–	NR	2FC	–	Died	8.6
16	Pred	NR	–	–	Died	20.6
17	–	NR	1MINE	–	Died	2.0
18	Pred	PR	5FCD+1COP+1RFD	PR	Died	34.5
19	Pred	CR	5FC+1FC+RCHOP	PR	Survived	97.3
20	Dxm	PR	12CHOP+8CP	PR	Died	102.4

CHOP = cyclophosphamide +adnamycin + vincrestine + prednisone, COP = cyclophosphamide +vincrestine + prednisone, CP = cyclophosphamide +prednisone, CR = complete remission, Dxm = dexamethasone, EPOCH = VP16+prednisone+vincrestine+cyclophosphamide+adnamycin, FC = fludarabine + cyclophosphamide, FCD = fludarabine + cyclophosphamide + dexamethason, Hyper CVAD+R = cyclophosphamide+vincrestine+cytarabine+dexamethasone+rituximab, MINE, NR = no remission, PR = partial remission, Pred = prednisone, RCHOP = rituximab + cyclophosphamide + adnamycin +vincrestine + prednisone, RCOP = rituximab + cyclophosphamide + vincrestine + prednisone, REPOCH = rituximab+VP16+prednisone+vincrestine+cyclophosphamide+adnamycin, results1 = efficacy for NHLs, results2 = efficacy for AIHA, RFC = rituximab + fludarabine + cyclophosphamide, RFD = rituximab + fludarabine + dexamethason, RFD = rituximab + fludarabine + dexamethason, survival time = time to start with the first disease (maybe AIHA, or NHL) and end with the patient's death, treatment 1 = treatment for NHLs, treatment 2 = treatment for AIHA.

respectively, and patients 19 and 20 had CLL/SLL, which is an inert lymphoma with a long survival period.

4. Discussion

Lymphomas frequently co-exist with AIHA,[2–4] with 20% of AIHA patients and 7% to 10% of lymphoma patients presenting the other disease.[2,3,11,12] Our cohort of 20 patients accounted, respectively, for 0.91% and 9.8% of the initially diagnosed NHL and AIHA patients. The lower incidence of AIHA/NHL in this cohort could be due to regional and lifestyle factors. Furthermore, AIHA patients often do not seek medical attention due to the mild symptoms, whereas the presence of both AIHA and NHL may make the patient despondent and unwilling to get treatment.

Although AIHA can occur with almost all types of NHLs,[2–4] our cohort mainly included patients with DLBCL, CLL/SLL, MZBL, AITL, MCL, ALCL and PTCL, with the highest incidents in AITL, MZBL, and BCL-U. To the best of our knowledge, this is the first report of AIHA incidence in each NHL subtype. Previous studies have reported AIHA in 5% to 10% CLL/SLL patients, and implicated it as one of the causes of CLL/SLL.[18–20] In our cohort however, AIHA was diagnosed in 3 of the 5 CLL/SLL patients only after multiple courses of chemotherapy, indicating that AIHA was probably the result of chemotherapy. Therefore, we surmise that unlike in Europe and USA where AIHA is often the cause of CLL, it is secondary to CLL/SLL treatment among Chinese patients with no prior history of the disease.

AIHA/NHL is significantly correlated to older median age, tumor stage IV, and multiple NHLs.[3,11] We further detected a 66.7% incidence of LBMI in AIHA/NHL patients, which could be due to the inherently high incidence of LBMI among these patients, simultaneous BMS and BMB that reduces missed diagnosis rate, and the tendency of patients to seek treatment only when their condition aggravates.

At present, PET/CT, BMS, and BMB are used to detect LBMI. PET/CT scan has high sensitivity, but insufficient specificity. In addition, BMB shows better diagnostic results compared to BMS.[21,22] Karak et al[21] proposed PET/CT scan to detect LBMI in DLBCL patients, followed by routine BMS if the scan is diffuse positive, BMB or BMS if it is positive, and neither if the scan is negative. Since only some patients in our cohort underwent PET/CT scans, we focused only on the diagnostic value of BMB and BMS, and observed inconsistent results across 10 patients with LBMI. This strongly suggests that the distribution of NHL lesions in AIHA/NHL patients is uneven, and BMB or BMS alone would result in a relatively higher missed diagnosis rate. Therefore, we recommend the method suggested by Karak et al if PET/CT scans are available; otherwise, BMB and BMS should be performed simultaneously to minimize missed diagnosis of LBMI. The latter approach is particularly suitable for economically underdeveloped areas.

The pathogenesis of AIHA/NHL is still unclear,[2,3,7,8] although recent studies have implicated chronic antigen stimulation and the formation of autoantibodies.[2,3] Drug-induced autoantibody formation is a major factor driving AIHA,[23–25] and likely involves perturbation in the different lymphocyte subtypes.[21–23] Rituximab induces AIHA by destroying the $CD20^+$ B cells, and triggering the release of pro-inflammatory IL-6 and production of autoreactive plasma cells that are resistant to red blood cells.[23,24] Fludarabine mainly targets the CD4+ T cells, and promotes expansion of self-reactive T cells[25].

The treatment of AIHA/NHL is incumbent on the initial diagnosis. If both are diagnosed at the same time, NHL treatment by chemotherapy and surgery can control the progression of both.[26–28] However, the therapeutic outcomes are at present unsatisfactory for AIHA/NHL patients,[29] and novel methods need to be explored. In our cohort, only 2 of the 7 patients that completed the chemotherapeutic regimen achieved CR. We believe that glucocorticoid administration can be considered for AIHA/NHL patients in the absence of any other options. It is important to devise more individualized chemotherapy regimens against NHL in these patients.

Our study had some limitations that should be addressed. First, 47 NHL patients could only be diagnosed as BCL rather than the exact NHL type, which may have affected the incidence of AIHA/NHL across the different types. Second, only 7 patients received standardized NHL treatment, which makes it impossible to determine the clinical outcome of AIHA/NHL.

5. Conclusions

AIHA can co-exist with various NHLs and the defining clinical characteristic of AIHA/NHL is the high incidence of LBMI. Simultaneous BMS and BMB are recommended to avoid missed diagnosis.

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