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Original Article

Classical Hodgkin lymphoma with necrotic granuloma-like morphological features

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Abstract: *Aims:* To summarize and elucidate the clinicopathological characteristics of Necrotic Granuloma-like Hodgkin Lymphoma (NGHL), which is a classical Hodgkin lymphoma (CHL) with uncommon morphologic features that are rich of tumor cells and has particular necrotic granuloma-like lesions. *Methods and Results:* Thirty-four cases of NGHL were selected from 1887 Hodgkin lymphoma, accounting for 1.8% (34/1887). The HE staining slides were reviewed and Immunohistochemistry (IHC) and Epstein-Barr Encoded RNA in situhybridization (EBER) were performed. Most patients were young with slight females predominance (Median age, 25.5 years; Range, 10-68 years; M:F 1:1.6). Fifteen patients (44.1%) had B symptoms. The common involvement sites were cervical lymph nodes (91.2%) and mediastinum (61.8%). Morphologically, NGHL had multiple necrosis foci surrounded by plenty of cluster and cohesive large tumor cells, forming necrotic granuloma-like lesions. Tumor cells were almost limited around necrosis foci. Between the necrosis foci, there was heterogeneous admixture of non-neoplastic cells that were predominantly mature small lymphocytes. There was no obvious fibrosis in all cases. All cases had the typical immnophenotypes of CHL, which was positive for CD30 and weak positive for PAX-5. EBER was positive in 26.1% cases (6/23). Thirty-one patients were followed for 4-146 months (median: 37 months), and five-year overall survival rate was 75.5%, which was worse than in classical HL. The 5-year survival rate for stage I-II and stage III-IV patients were 100% and 50.4% respectively, and the difference had statistical significance. *Conclusions:* NGHL had unique morphology and clinical features, which were different from typical CHL, and may be a variant of MCCHL.

Keywords: Hodgkin lymphoma, necrotic granuloma-like, morphological variant

Introduction

Hodgkin lymphoma (HL) is a monoclonal lymphoid neoplasm (in most instances derived from B cells), characterized by a minor population of tumor cells scattered in an abundant heterogeneous admixture of non-neoplastic inflammatory and accessory cells. Typically, the neoplasm cells are only 0.1% to 10% of the entire mass and in scattered distribution [1]. HL is divided into two major entities, lymphocyte-predominant and classical Hodgkin lymphoma (CHL). The latter one further subtyped into nodular sclerosis (NS), lymphocyte-rich (LR), mixed cellularity (MC) and lymphocyte depleted (LD). However, we noticed that some rare CHL cases have typical Hodgkin and Reed-Sternberg (HRS) cells with immunophenotype of CHL, but HRS cells comprise more than 10% of the entire tumors and cohesively distribute around the necrosis foci, forming necrotic granuloma-like lesions. We temporarily name these tumors as necrotic granuloma-like Hodgkin lymphoma (NGHL). These cases neither have nodular sclerosis nor lymphocyte-depleted background. They are difficult to be subclassified into any subtypes. Based on the current subclassification guidelines, NGHL can be set into mixed cellularity classical Hodgkin's lymphoma (MCCHL), but these cases have the special morphological characteristics that are different from typical MCCHL. Simultaneously, since the granuloma-like morphology and cohesive distribution of HRS cells, they are easy to be confused with some non-neoplastic granulomatous lesions or non-Hodgkin large cell lymphomas. In present study, we described 34 such cases and documented their unusual morphologic and clinical features.

Table 1. Primary antibodies and conditions used for IHC staining

Antibody	Clone	Dilution	Antigen Retrieval	Source
CD20	L26	1:200	HP EDTA*	Maixin. Bio
CD3	SP7	1:100	HP EDTA*	Maixin. Bio
CD30	Ber-H2	1:20	HP EDTA*	Maixin. Bio
CD15	Carb-3	1:20	HP EDTA*	Maixin. Bio
CD68	KP1	1:30	HP EDTA*	Maixin. Bio
LCA	PD7/26 + 2B11	1:100	HP EDTA*	Maixin. Bio
BCL-6	LN22	1:20	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
OCT-2	OCT-2	1:20	HP EDTA*	Maixin. Bio

*HP EDTA: Boiling with EDTA (1 mM pH9.0) under high pressure.

Patients and methods

Patient population

The cases were selected from the 25641 hematopoietic and lymphoid tissue disorders consultation cases that were diagnosed between January 2002 and November 2016 at the Pathology Department of Beijing Friendship Hospital/the Lymphoma Diagnosis Research Center of Beijing Institute of Clinical Medicine (A large lymphoma consultation center in China). Beijing Friendship Hospital Ethical Committee Approval (2016-P2-032-01) was acquired for the review and analysis of patients' data. Among them, 14512 (56.6%) cases were diagnosed as lymphoma. In these lymphoma cases, 1887 (13%) cases were diagnosed as HL. Thirty-four cases of NGHL were collected based on the the following criteria: (1) HL cells associated with necrosis and granuloma-like morphologic features (as described in the result); (2) Neither sclerotic fibrosis nodule nor marked capsule thickening present, which is the structural characteristic of NSCHL; (3) No lymphocyte-depleted background; (4) Excisional biopsy only; (5) No treatment history or immunodeficiency disorders. Moreover, we also random selected 65 cases typical MCCHL as comparison.

Clinical information collection

The clinical records and follow-up data were retrieved through the pathology electronic archives of the Lymphoma Diagnosis Research Center, including the patient's age, gender, symptoms, sites of involvement, clinical staging, therapeutic process and the original pathological diagnosis results. The tumor staging was performed using Ann Arbor staging criteria [2].

Immunohistochemistry (IHC) and in situ hybridization for EBV-encoded RNA (EBER)

IHC: MaxVision™ 2 kit (catalog No. KIT-5910/5931) and monoclonal antibodies, including CD20, CD3, CD30, PAX5, CD15, LCA, MUM-1, Ki-67, provided by Maixin Biotech (Fuzhou, China), were used for the detection of all relevant antigens according to the established method [3]. The pretreatment methods as well as primary antibodies and their working dilutions used in this study are listed in **Table 1**.

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 min; (3) Hybridization with digoxigenin-conjugated EBV (EBERs) probe at 37°C for 4 h; (4) Signal detection using peroxidase-conjugated anti-digoxigenin antibody and 3,3'-diaminobenzidine; and (5) Counterstaining of sections with hematoxylin solution. The positive signals were brownish yellow and localized within the nuclei. The known EBER-positive case of extranodal NK/T-cell lymphoma and EBER-negative case of lymphoid hyperplasia of the tonsil were designated as positive and negative controls, respectively.

Follow-up

Evaluation of recent curative effect was adopted from Cheson Efficacy Criteria of malignant lymphoma [4]. According to the response to initial therapy, all patients were divided into the complete remission (CR) and the non-CR group. Survival time was measured from the date of diagnosis to the death of any causes or to the last follow-up visit. The follow-up deadline was December 20, 2016.

Statistical analysis

Statistical analysis was performed with the SPSS 20.0 software. Chi-squared Test or Fisher's Exact Test was used to compare the

Table 2. The clinical features and follow-up data of NGHL

Case No.	Age (y)	Gender	duration of symptoms (mo)	Systemic Symptoms			Skin Pruritus	Sites of involvement				Stage	Treatment	Response	Clinical Status
				Fever	Night Sweat	Weight loss		Mediastinum	Peripheral Lymphoid Organs	Sites of Extranodal	Bone Marrow				
1	26	F	1	+	-	-	-	-	+ (C, A)	NA	NA	NA	NA	NA	MV
2	22	M	1	+	-	-	-	+	+ (C, S, AP)	PC	+	IV	CT + RT	PD	D
3	27	F	2	-	-	-	-	+	+ (C, HL)	-	-	II	CT + RT	CR	TFS
4	23	F	7	+	-	-	+	+	+ (C, SC, S, AP)	SL	+	IV	CT	PD	D
5	29	F	6	-	-	-	-	-	+ (C, SC)	-	-	II	CT + RT	CR	TFS
6	25	F	11	-	-	-	-	+	+ (C, SC, RP)	-	-	III	CT + RT	CR	TFS
7	23	M	14	+	+	-	+	+	+ (SC)	NA	NA	NA	NA	NA	MV
8	10	F	2	+	-	-	-	+	+ (C, A, I, RP)	-	-	III	CT + RT	PD	TWS
9	27	M	6	-	-	-	-	+	+ (C, A, I, S, AP)	-	-	III	CT + RT	PD	D
10	22	F	1	-	-	-	-	-	+ (C)	-	-	I	CT + RT	CR	TFS
11	27	F	3	-	-	-	-	-	+ (C, SC)	-	-	II	CT	CR	TFS
12	20	F	1	-	-	-	-	-	+ (C)	-	-	I	CT	CR	TFS
13	22	F	4	+	+	+	-	-	+ (C, SC)	-	-	II	CT	CR	TFS
14	24	F	5	-	-	-	-	+	+ (C, A, I, SM, S)	-	-	III	CT	CR	TFS
15	23	F	13	-	-	-	-	-	+ (C, A)	-	-	II	CT	CR	TFS
16	24	M	1	-	-	-	+	+	+ (C)	-	-	II	CT	CR	TFS
17	56	M	4	+	-	+	-	+	+ (I, AP)	-	-	III	CT	CR	TFS
18	25	F	4	+	-	-	-	+	+ (C, A, HL, S)	DL	-	IV	CT	PD	TWS
19	26	F	3	-	-	-	-	+	+ (C, A, SC, AP)	-	-	III	CT	PD	D
20	30	F	6	-	-	-	-	+	+ (C, HL, AP)	DL	-	IV	CT	PD	D
21	60	M	12	+	-	-	-	-	+ (C, I, S, AP)	-	-	III	CT + RT	PD	D
22	28	M	1	-	-	-	-	-	+ (C, A)	-	-	II	CT	CR	TFS
23	64	M	36	-	-	-	-	-	+ (C)	-	-	I	CT	CR	TFS
24	21	M	1	-	-	-	-	+	+ (C)	-	-	II	CT	CR	TFS
25	27	F	3	+	+	+	-	-	+ (C, SC, HL, AP)	-	-	III	CT + ASCT	CR	TFS
26	21	F	11	+	+	+	+	+	+ (C, SC, S)	-	-	III	CT + RT	CR	TFS
27	26	M	2	-	-	-	+	-	+ (C, HL)	NA	NA	NA	NA	NA	MV
28	44	F	1	-	+	-	+	+	+ (C, SC, RP)	DL	-	IV	CT	PR	TWS
29	68	M	4	+	+	+	-	+	+ (A, SC, I, S)	-	-	III	CT	SD	TWS
30	30	M	2	-	-	-	-	-	+ (C)	-	-	I	CT + RT	CR	TFS
31	11	F	1	+	-	-	-	+	+ (C)	-	-	III	CT	PD	TWS
32	30	M	6	+	-	-	-	+	+ (C, A, HL, S)	PC	-	III	CT	PR	TWS
33	24	F	4	-	-	-	-	+	+ (C, SC)	PC	-	II	CT	PR	TWS
34	15	F	0.5	-	-	-	-	+	+ (C)	-	-	II	CT	PR	TWS

Notes: NA, not available. A, Axillary; C, cervical; I, inguinal; SC, supraclavicular; RP, retroperitoneal; HL, hilar of lung; AP, abdominal and pelvic cavity; SM, submandibular; S, spleen. PC, pericardial cavity; SL, single lung; DL, double lung; CT, chemotherapy; ASCT, autologous stem cell transplantation; RT, radiotherapy; CR, complete remission; PR, partial remission; PD, disease recurrence or progression; SD, stable disease; MV, missing visits; D, dead; TFS, tumour-free survival; TWS, tumor-with survival.

Table 3. Comparing of clinical information between NCRHL with MCCHL

Group	*n*	Gender M/F	Age <30/≥30	B symptom n (%)	Mediastinum involved n (%)	Sleen involved n (%)	Extranodal involved n (%)	Stage I-II/III-IV
NGHL	34	13/21	26/8	15 (44)	20 (58.9)	9 (26.5)	7/24*	14/17*
MCCHL	65	44/21	30/35	31/(47.8)	16 (24.6)	5 (7.7)	8/57	43/22
χ^2 value		7.930	8.351	0.115	11.289	6.483	1.680	3.835
P value		0.005	0.004	0.735	0.001	0.011	0.195	0.050

*After excluding the cases lack of related information.

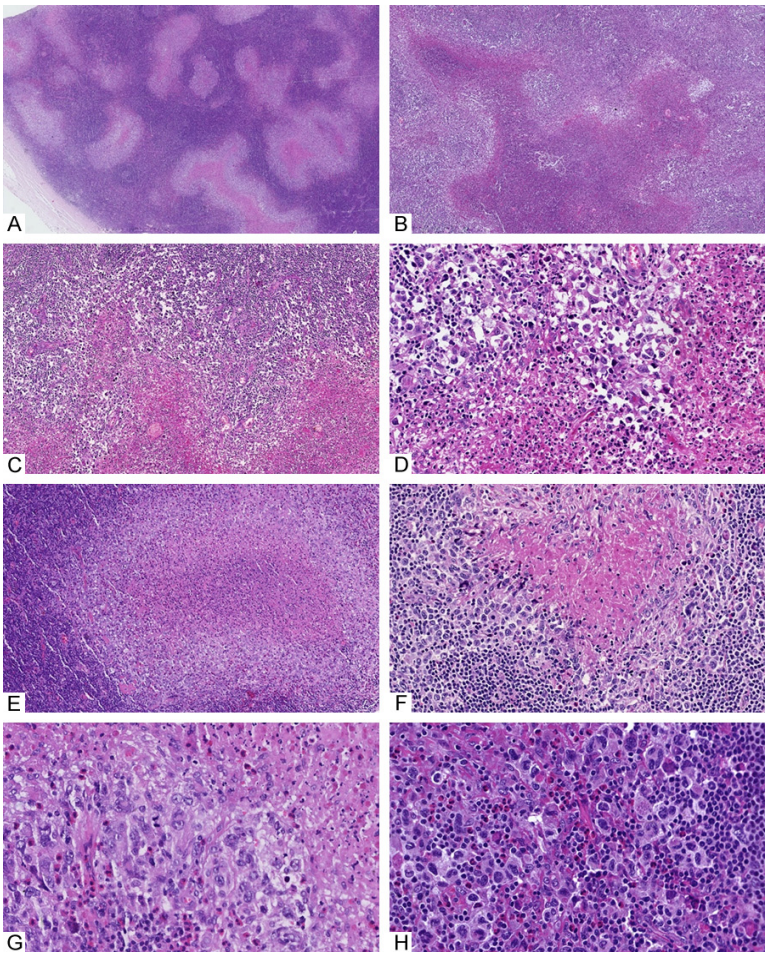

Figure 1. The morphologic features of Necrotic Granuloma-like Hodgkin Lymphoma (NGHL). (A) Lymph node biopsy showed scattered multifocal pale staining nodules, a large number of lymphocytes between nodules and was no sclerosis nodule, with a mild thickened capsule. (B) The large sheet or map-like necrotic focus. (C, D) Cohesive clusters and sheets of large malignant cells (middle) around the necrotic focus (below). (E, F) The necrosis focus. There were plenty of neutrophiles and karyorrhexis in the centre area. A large number of tumor cells surrounded the necrotic focus that showed necrotic granuloma-like change. (G, H) All kinds of HRS cells and anaplastic large malignant cells could be seen. [hematoxylin and eosin (HE) staining; The images were scan by Hamamatsu NanoZoomer Whole Slide Scanner. Original magnifications ×20 (A), ×40 (B), ×100 (C, E), ×200 (D, F), and ×400 (G, H)].

frequency between different groups. Survival curves were drawn using Kaplan-Meier method and Log rank test was performed. *P*-value less than 0.05 is defined as statistical significant for all tests.

Results

Clinical data

Thirty-four patients of NGHL were indentified in this study, accounted for 1.8% (34/1887) of all HL cases. The ratio of male to female was 1:1.6. The median age was 25.5 years (range: 10-68). Twenty-six (76.5%) patients were between 20 to 30 years old. No one had the autoimmune diseases, organ transplantation or immunodeficiency disease history. B symptoms (fever, drenching of night sweats, significant body weight loss) were present in 15 of 34 patients (44.1%). Six cases (17.6%) had skin pruritus. All 34 cases had lymph nodes enlargement, predominately involving cervical region lymph nodes (31/34, 91.2%). Mediastinal involvement was presented in 21 cases (61.8%). Spleen involvement was reported in 9 cases (29.0%, 9/31). Nine cases had other extranodal sites involvement, including lung (12.9%, 4/31), pericardial cavity (9.7%, 3/31), and bone marrow (6.5%, 2/31). Stage I-IV patients were 4 (12.9%), 11 (35.5%), 11 (35.5%), and 5 (16.1%), respectively. All details were listed in **Table 2**. Comparing with typical MCCHL patients, NGHL

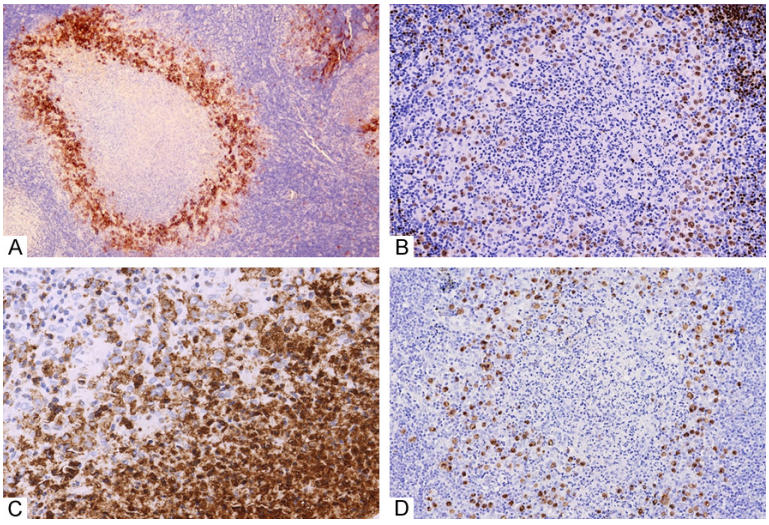

Figure 2. IHC and ISH staining of NGHL. The tumor cells were strongly positive for CD30 (A), weakly positive for PAX5 (B), partially positive for CD15 (C) and EBER (D). [The images were scan by Hamamatsu Nano Zoomer Whole Slide Scanner. Original magnifications ×100 (A), ×200 (B, D), and ×400 (C)].

patients were younger, more female and more patients had mediastinum and spleen involvement. All the differences were statistic significant (**Table 3**).

All of the cases were consultation cases and 27 cases had the original pathological diagnosis that had been reported by the referring laboratories. Only 12 cases (44.4%) were originally diagnosed as CHL or suspicious CHL. Other 15 cases (55.6%) were misdiagnosed. Specifically, 6 cases were originally misdiagnosed as non-Hodgkin lymphoma [two diffuse large B-cell lymphoma (DLBCL); one anaplastic large cell lymphoma (ALCL); one B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL; two non-Hodgkin's lymphoma, unclassifiable]. One case was misdiagnosed as mesenchymal sarcoma and 8 cases were misdiagnosed as benign lesions (Kikuchi's Disease in 3 cases; cat-scratch lymphadenitis in 3 cases; tuberculosis lymphadenitis in 1 case; chronic lymphadenitis in 1 case).

Morphological features

All 34 samples were lymph nodes excisional biopsies. The lymph nodes architectures were completely (23 cases) or partially (11 cases) effaced. The capsules were mildly thickened in 12 cases. In 5 cases, there was mild proliferation of interstitial fibrosis and/or focal mild fibrosis, but there was no nodular sclerosis in all cases. Besides these, all of the cases had two main morphological characteristics as following.

First one was necrotic granuloma-like change. In the low magnification, there were multifocal pale staining nodules that were similar with granulomatous nodules. They had central coagulation necrosis, some even had large sheet or map-like necrosis. Some nodules fused together. In the necrosis areas, there were massive neutrophils infiltration, a little eosinophilic nuclear fragmentation and/or a few degenerated eosinophils. Around the necrotic foci, there were cohesive-distributed dysplastic large cells. The tending of the radial arrangement could be seen in 4 cases. Around the necrotic granuloma-like nodules, there were abundant heterogeneous admixture of non-neoplastic inflammatory and accessory cells that were predominantly mature small lymphocytes, mixed with variable amount of eosinophils, neutrophils, histocytes and plasma cells. Eosinophils and/or neutrophils frequently presented at the tumor cells rich areas (**Figure 1A-F**). There was no sinus infiltration of tumor cells in all cases.

Second, all patients had clusters of tumor cells arranged in sheets or groups that were more than 10% of the total infiltrated cells. Unlike the typical morphology of HL that tumor cells are scattered in background cells, the tumor cells predominantly distributed around the necrotic nodules as the cohesive clusters. All kinds of HRS cells could be seen, included Hodgkin-like cells, R-S cells, mummified cells, lacunar cell-like cells and anaplastic large cells (**Figure 1G**, **1H**). There was no sarcoma-like spindle cell morphology.

*The immunophenotypes and in situ hybridization (ISH) for EBER (**Figure 2A-D**) (**Table 4**)*

In all 34 cases of NGHL, tumor cells were positive for CD30 (34/34, 100%), weakly positive for Pax-5 (34/34, 100%). The majority cases

Table 4. 34 cases of NGHL: immunophenotypic features and EBV status

No.	Age	Gender	CD30	CD15	CD20	pax-5	Mum-1	LCA	CD3	EBER
1	26	F	+	+	-	+ (d)	NA	-	-	NA
2	22	M	+	-	+ (d) (p)	+ (d)	NA	-	-	-
3	27	F	+	-	-	+ (d)	NA	-	-	NA
4	23	F	+	-	+ (d) (p)	+ (d)	NA	-	-	-
5	29	F	+	-	-	+ (d)	NA	-	-	-
6	25	F	+	-	-	+ (d)	NA	-	-	-
7	23	M	+	+ (p)	-	+ (d)	NA	-	-	+
8	10	F	+	+	-	+ (d)	NA	-	-	+
9	27	M	+	-	-	+ (d)	NA	-	-	NA
10	22	F	+	NA	-	+ (d)	NA	-	-	-
11	27	F	+	+ (p)	+ (d)	+ (d)	+	-	-	NA
12	20	F	+	NA	-	+ (d)	NA	-	-	NA
13	22	F	+	+	-	+ (d)	+	-	-	NA
14	24	F	+	+ (p) (d)	-	+ (d)	+	-	-	+
15	23	F	+	+	-	+ (d)	NA	-	-	NA
16	24	M	+	NA	+ (d) (p)	+ (d)	NA	-	-	NA
17	56	M	+	+	-	+ (d)	+	-	-	+
18	25	F	+	-	-	+ (d)	+	-	-	NA
19	26	F	+	-	-	+ (d)	+	-	-	-
20	30	F	+	-	-	+ (d)	+	-	-	-
21	60	M	+	+	+ (d)	+ (d)	+	-	-	+
22	28	M	+	+	-	+ (d)	+	-	-	-
23	64	M	+	+	-	+ (d)	+	-	-	+
24	21	M	+	-	+ (d)	+ (d)	+	-	-	-
25	27	F	+	-	-	+ (d)	+	-	-	-
26	21	F	+	+	-	+ (d)	+	-	-	NA
27	26	M	+	+	-	+ (d)	+	-	-	-
28	44	F	+	+	-	+ (d)	+	-	-	-
29	68	M	+	+	-	+ (d)	+	-	-	-
30	30	M	+	+	-	+ (d)	+	-	-	-
31	11	F	+	-	-	+ (d)	NA	-	-	-
32	30	M	+	-	-	+ (d)	NA	-	-	NA
33	24	F	+	+ (p)	+ (d)	+ (d)	+	-	-	-
34	15	F	+	+	-	+ (d)	NA	-	-	-

Notes: NA, not available; d, dim; p, partial.

were positive for CD15 (18 of 31 cases stained with CD15, 58.1%), 3 out of 7 cases stained with Oct-2 were positive (42.9%), MUM-1 was strong positive in all 18 cases that had been stained (18/18, 100%), Ki-67 index was more than 90% in all the cases. CD20 partially dimly expressed in 7 cases (20.6% 7/34). Tumor cells were negative for LCA, CD2, CD3, CD43, CD68, Bcl-6, Granzyme-B, ALK and EMA. In 23 cases were tested for ISH of EBER, 6 cases (26.1%) were positive (**Figure 2D**). EBER was positive in 68.9% (42/61) MCCHL cases and the difference had statistical significance (x^2=12.473, P<0.01).

Follow-up

Of the 34 patients, 31 patients (91.2%) were followed up for 4 to 146 months (median: 37 months; average: 47.5 months). All patients received HL-standard chemotherapy regimen, named ABVD (adriamycin, bleomycin, vinblastine, darcarbacine) for 4 to 22 circles. Following the ABVD chemotherapy, 3 patients received chemotherapy regimen of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) for 2 to 4 circles, 2 patients used the treatment regimen of CHOP (cyclophosphamide, Hydroxydaunorubicin, oncovin, prednisone) for 2 or 3 circles, 9 patients received local radiotherapy, and 1 patient received autologous stem cell transplantation. After the initial chemotherapy, CR was seen in 17 patients (54.8%), partial remission (PR) was seen in 4 patients (12.9%), disease recurrence or disease progression was seen in 9 patients (26.5%), and 1 patient still was in disease stabilization (2.9%). The CR rates for stage I, II, III and IV patients were 100% (4/4), 72.7% (8/11), 45.5% (5/11) and 0 (0/5), respectively. The proportion of CR had statistical significant difference (P=0.008, Fisher's Exact Test) among four stages patients.

In the whole series of follow ups, 6 patients (19.4%) died of HL from 4 to 71 months after diagnosis, 9 patients (29.0%) had survived with tumor, and 16 patients (51.6%) survived free of tumor (**Table 2**).

Prognostic factor analysis

Compared with the CR group, non-CR group patients mostly presented with B symptoms ($P<0.05$), mediastinal involvement ($P<0.01$), and splenic involvement ($P<0.05$). In addition, they were significantly related to the external invasion of lymph nodes ($P<0.05$) and the high proportion ($P<0.01$) of stage III to IV. It wasn't correlated with patient's age and gender ($P>0.05$).

The 5-year overall survival (OS) rate of NGHL patients was 75.5%. The 5-year overall survival rate of stage I-II was 100%, and the 5-year overall survival rate of stage III-IV was 50.4%, and the Log-rank test showed that the difference had statistical significance ($x^2=7.520$, $P=0.007$). The 5-year overall survival rate had no statistical significant difference between NGHL with typical MCCHL groups ($P>0.05$).

Discussion

The 34 cases in this study represented a previously unrecognized morphological variant of CHL. Based on our data, NGHL is rare (1.8% of the HL patients) and frequently happens in 20-30 year old persons (76.5%) and has 5-year OS rate of 75.5%, which is worse than typical CHL in China (97.7%) [5]. In contrast to the typical CHL, they have increased numbers of tumor cells (more than 10% of total cells in the lesion) with cohesive and cluster distribution. The tumor cells distribute around the necrosis to form granuloma-like lesions that could be misdiagnosed as benign granuloma lesions. In the literature, the massive neutrophilic infiltration and necrosis in HL have been described by several authors [6-8]. Due to the presence of the sclerosis nodular, all of these cases were subclassified into NSCHL. In addition, necrosis can be a rare complication that may occur in patients diagnosed with HL, as a result of treatment [9]. All of our cases showed NGHL morphologic features without chemotherapy history. The syncytial growing pattern of HRS cells in HL was also described in a few literatures [10, 11]. They emphasized that these tumors had the overlap characteristics of HL and ALCL or DLBCL. Some of the cases were confirmed as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL. Actually, in uncommon cases of NSCHL that were reported in literature, tumor cells may form prominent cellular aggregates, which may be associated with necrosis and a histocytic reaction, resembling necrotizing granulomas. These tumors were called as syncytial variant of NSCHL [12-14]. In contrast with this tumor, all of our cases didn't have the sclerosis nodular and most of cases even did not have the thickened lymph node capsule or fibrosis. In our review of the literature, the clinicopathological features of NGHL have still not been clearly recognized so far.

NGHL patients were typically young adults and most were in twenties (76.5%), with a slight female predominance. Bimodal age curve doesn't present as the typical CHL [15, 16]. NGHL has the basic morphological and immunophenotypic features of CHL [17]. However, NGHL can't be classified into NSCHL, for no nodular sclerosis (one of diagnostic criteria of NSCHL: the broad fibroblast-poor collagen bands surround at least one nodule [1]), although NSCHL may present with rich tumor cells and necrotic granuloma-like background [12, 18, 19]. In LDCHL, HRS cells may predominate as we have seen in NGHL. However, the tumor always produces a sarcomatous appearance and has lymphocytes-depleted background, even presents with diffuse fibrosis [20]. All of our cases had lymphocytes predominant background between the necrotic foci. Furthermore, based on the current subclassification guidelines, NGHL can be set into MCCHL. But these cases have the special morphological characteristics that didn't be described in MCCHL. Therefore, we considered that NGHL might be a new variant of MCCHL. In addition, a proposal from the International Lymphoma Study Group was that MCCHL might be a real disease type, and the cases which cannot be classified because of special histological features should be classified as CHL-unclassifiable [1, 18, 21]. Therefore, NGHL also could be a new subtype of CHL [22].

NGHL is rare and has not been sufficiently learned yet. Therefore, many cases were misdiagnosed (55.6% cases were misdiagnosed initially in our series) as either NHL or non-neoplasm granuloma lesions. NGHL does have some overlapping histopathological findings with these lesions and easy to be confused, so, the differential diagnosis is very important. (1) ALCL: both ALCL and NGHL may present with anaplastic large cells and HRS-like cells. But

morphologically, the neoplastic cells typically grow within sinuses and/or around vessels in ALCL. In contrast, in NGHL, the neoplastic cells grow around necroticnodules. In terms of immunophenotype, the two tumors can be distinguished by PAX5 expression in the HRS cells of NGHL and expression of T cells/cytotoxic molecules and/or ALK in tumor cells of ALCL [23-26]. NGHL may positive for EBER that should be negative in all cases of ALCL [27]. (2) Primary mediastinal large B-cell lymphoma (PMBL): This tumor occurs predominantly in young females who presents with mediastinal mass, and can have pleomorphic and/or multilobated nuclei which may resemble HRS cells and raise suspicion of HL. However, PMBL brightly expresses B-cell antigens and LCA, which are all negative in NGHL. CD30 can be positive in both tumors, but usually weaker and heterogeneous in PMBL. EBV can be positive in NGHL, but is barely positive in PMBL. (3) B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL: This tumor and the NGHL can be confused in morphology that presents with necrosis and HRS-like tumor cells. However, the infiltration of abundant neutrophils in necrosis is usually found in NGHL, but is rare in B-cell lymphoma, unclassifiable. This tumor also brightly expresses B-cell antigens and LCA, which are all negative in NGHL [28, 29]. (4) Non-neoplastic histocytic necrosis or granuloma lesions. Some benign lesions may have necrotic granuloma, including Kikuchi's disease, Cat-scratch lymphadenitis, tuberculous lymphadenitis, and so on. In these lesions, there are plenty of histocytes in and around the necrosis, rather than dysplastic tumor cells, and can be proved by immunophenotype that are positive for CD68, CD163 and low index of Ki-67. (5) Angioimmunoblastic T cell lymphoma (AITL). AITL may present EBV-positive RS-like cells of B-cell lineage, which could have same immunophenotype with CHL. However, AITL occurs in the middle-aged and elderly and presents with advanced stage disease. The tumor is frequently associated with increased follicular dendritic cell meshworks and RS-like large cells are strong positive for CD20, which are different with CHL. (6) Immunodeficiency-related B-LPD with CHL-like features. It may have the similar morphology with NGHL and even have the same immunophenotype. Therefore, when the tumor is positive for EBER, the clinical immunodeficiency history is the key to differentiate these two tumors.

Moreover, all NGHL patients that were followed-up received HL standard chemotherapy regimen, but the 5-year OS was 75.5%; 5-year OS for stage III-IV patients was only 50.4%. Both are much worse than typical HL patients in China (97.7%, 81.5%) [5, 30]. Based on our statistical analysis, worse prognosis is significantly related with the presenting B symptoms, higher stage and extranodal involvement. For best treatment efficacy, whether NGHL patients with these high risk factors should be treated with more aggressive regimen or not, this issue is to be solved by further research with a larger sample size.

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Disclosure of conflict of interest

None.

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