Original Article

Primary Intestinal NK/T Cell Lymphoma: A Clinicopathologic Study of 25 Chinese Cases

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Abstract

Background: Primary intestinal NK/T cell lymphoma is extremely rare and early diagnosis is frequently difficult. The aim of this study is to investigate the clinicopathological findings, immunophenotype, and T cell receptor (TCR) γ gene rearrangement of primary intestinal NK/T cell lymphomas in 25 Chinese cases.

Methods: Clinical data of the 25 cases were analyzed. Immunohistochemistry for immunophenotype, in situ hybridization for EBER, and polymerase chain reaction for TCR γ gene rearrangement were investigated. Survival curves according to clinical characteristics were analyzed.

Results: The median age was 33 years and the median survival was 7 months. The common symptoms consisted of abdominal pain, fever, marasmus, diarrhea, and hematochezia. Endoscopically, the tumors were mainly featured by focal, multifocal or diffuse irregular ulcers, which most frequently emerged in the ascending colon. Histologically, the tumors were characterized by the proliferation of pleomorphic atypical lymphoid cells (ALCs), necrosis, lympho-epithelial lesions, and mixed inflammatory infiltration. The positive frequency of CD3ε was 88.2%, of CD56 was 84%, granzyme B was 90%, and EBER was 84.2%. A total of 12 out of 14 cases (85.7%) highly expressed Ki67. The negative prognostic factors for survival were Ann Arbor stage IIIE or IVE ($P = 0.039$) and more than one extranodal site of disease ($P = 0.019$).

Conclusion: Primary intestinal NK/T cell lymphomas most frequently favor young people and have a poor prognosis. Due to the nonspecific clinical and endoscopic findings, it is difficult to distinguish intestinal NK/T cell lymphomas from inflammatory and infectious disorders. Histopathology, immunophenotype, and DNA study play key roles in differential diagnosis.

Keywords: Herpes virus 4, human, immunophenotyping, intestines, lymphoma

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Introduction

Primary intestinal lymphoma is defined as an extranodal lymphoma arising in the intestine, with the bulk of disease localized to this site. Extranodal NK/T cell lymphoma is a subgroup of cytotoxic T or NK cell lymphomas having a multiple morphologic spectrum which originates outside the lymph node. NK/T cell lymphoma accounts for 2% to 8% of non-Hodgkin lymphomas (NHL) in Asia,[1–3] where it shows its highest prevalence. In Europe it comprises less than 2% of all NHL cases.[1] Primary intestinal NK/T cell lymphoma is extremely rare. Since the early diagnosis of this lymphoma always presents difficulties to physicians, appropriate treatment might be delayed. In this study, we retrospectively analyze the clinicopathological features, immunophenotype, and T cell receptor (TCR) γ gene rearrangement of 25 Chinese cases with primary intestinal NK/T cell lymphomas to improve our understanding of this neoplasm.

Patient population

Clinical records of 25 hospitalized patients were collected from the West China Hospital of Sichuan University between May 1999 and May 2010. Histopathologic diagnosis of primary intestinal NK/T cell lymphoma was based on the new World Health Organization classification of lymphomas.[4] The Ann Arbor criteria was used for clinical staging.

Immunohistochemistry

Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections by the streptoavidin biotin peroxidase (SP) method. A panel of primary antibodies to: CD3ε (1: 200, Dakopatts, Denmark), CD20 (1: 200, Dakopatts, Denmark), CD56 (1: 50, Monosan, the Netherlands), granzyme B (1: 200, Culter, USA), and Ki67 (1: 100, Dakopatts, Denmark) were used. The SP kit and basic DAB detection system (Dakopatts, Denmark) were used for the remainder of the procedures. For the negative control, the primary antibody was substituted with PBS.

In situ hybridization

In situ hybridization was carried out with EBER (EBER1 and EBER2) oligonucleotide probes labeled with fluorescein isothiocyanate (FITC; Y017, Dakopatts, Denmark). Rabbit anti-FITC antibody conjugated with alkaline phosphatase (Dakopatts, Denmark) was used in combination with the probe and nitro blue tetrazolium (NBT)/5-bromo-4-chloro-3-indolyl phosphate (BCIP) as a substrate. A case of nasal NK/T cell lymphoma previously demonstrated to harbor EBV was used as the positive control. For the negative control, the probe was substituted with diethyl pyrocarbonate (DEPC).

Polymerase chain reaction (PCR)

The paraffin tissue DNA was prepared with a tissue DNA extraction and purification kit (Dneasy™ Tissue Kit, Qiagene). Two

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sets of primers were used to amplify the rearranged TCR γ gene as previously described.[5] A T cell lymphoma case with a known monoclonal rearrangement was used as the positive control, and a reaction without template DNA was simultaneously run as the negative control.

Statistical analysis

Overall survival (OS) was measured from the date of diagnosis to the date of death or the last follow-up visit. Survival curves were derived by the Kaplan and Meier method. Survival curves were plotted for gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, Ann Arbor staging, extranodal sites of disease, lactate dehydrogenase (LDH), and the International Prognostic Index (IPI). Univariate analysis of OS was performed using the log-rank test. Two-sided $P < 0.05$ were considered significant. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL).

Results

Clinical findings

Clinical characteristics at diagnosis, including gender, age, distribution of the ECOG PS, extranodal sites of disease, elevated LDH, and IPI score are listed in Table 1. The series comprised 16 men and 9 women, with a male to female ratio of 1.78:1. The median age was 33 years (range: 15 to 65 years). The mean interval between the time of symptom onset and that of lymphoma diagnosis was 6 months (range: 20 days to 3 years). Clinically, the most common symptoms were abdominal pain (60%), fever (56%), weight loss (56%), diarrhea (36%), and hematochezia (32%). The main complications were bowel perforation (16%), intestinal obstruction (12%), and gut hemorrhea (4%). None of the patients had either malabsorption or proven celiac disease before presentation.

Pathological features

Gross appearance

The tumors occurred from the duodenum to the rectum, while the most common site was the ascending colon, followed by the ileocecum and sigmoid colon. The rectum was rarely involved (Table 2). Tumors in more than one site were observed in 9 of 25 patients (36%), while in 16 cases (64%) neoplasms were localized to one site. Tumors in 22 of 25 cases (84%) were focal, multifocal or diffuse pleomorphic ulcers (Figure 1), and some were accompanied by segmental gut stricture, while in 4 cases (16%) they were tumor masses (Table 2).

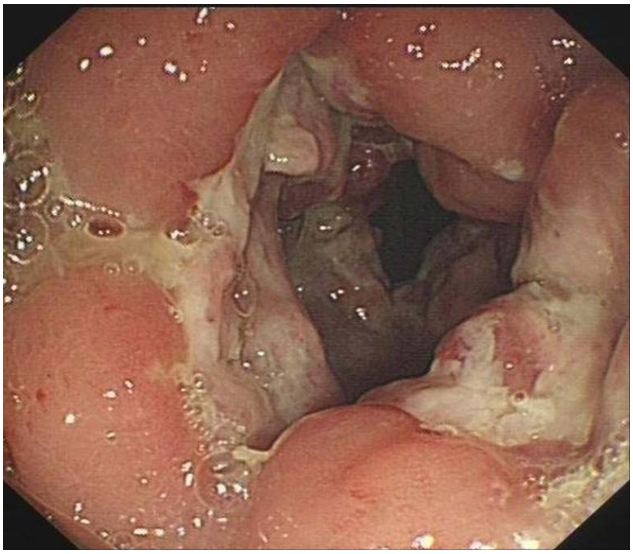

Figure 1. Diffuse irregular ulcers in the ascending colon.

Histological findings

Although small, medium, and large pleomorphic atypical lymphoid cells (ALCs) may be clustered or disseminated in the lesions, there were mostly medium or large cells in the majority of cases (Figure 2A). The ALCs had irregular nuclei and a pale cytoplasm. Mitotic changes were easily found. Most cases showed massive necrosis (Figure 2B) and lympho-epithelial lesions (LEL; Figure 2C), the latter were characterized by the invasion of ALCs into the mucosa and the destruction of mucosal glands. The neoplasms were admixed with varying proportions of inflammatory infiltrates; including small lymphocytes, plasmacytes, neutrophils, eosinophils, and histocytes. Angiocentric infiltrates were also found in some cases (Figure 2D).

Table 1. Relationship between clinical characteristics and the prognosis of primary intestinal NK/T cell lymphoma.

Characteristics	No. of patients	1-year OS (%)	*P*-value
Age (years)			
≤60	24	45	0.646
>60	1	0	
Gender			
Male	16	28	0.345
Female	9	50	
ECOG PS			
0–1	10	58	0.258
2–4	15	32	
Ann arbor staging			
IE or IIE	9	76	0.039
IIIE or IVE	16	17	
Extranodal sites of disease			
1	20	46	0.019
>1	5	0	
LDH			
Normal	19	54	0.066
Elevated	6	16	
IPI			
0–1	13	67	0.065
2–5	12	23	

ECOG PS=Eastern Cooperative Oncology Group Performance Status; LDH=lactate dehydrogenase; IPI=International Prognostic Index; OS=overall survival.

Table 2. Clinicopathological findings of primary intestinal NK/T cell lymphoma.

Case	Sex	Age	Location of lymphoma	Type of lymphoma	Stage	Complication
1	M	19	Jejunum	U	IV	B perforation
2	M	34	Jejunum	U	III	B perforation
3	M	20	Duodenum	U	IV	Gut hemorrhea
4	M	33	S. colon	U	II	None
5	F	30	S. colon, d. colon	U	IV	None
6	F	31	Ileocecum	TM	I	B obstruction
7	F	59	Duodenum	U	III	None
8	M	45	A. colon	U	I	None
9	F	20	S. colon	U	III	None
10	F	24	A. colon	U	IV	B perforation
11	M	33	Ileocecum	U	IV	B perforation
12	M	57	A. colon, ileocecum, terminal ileum	U	IV	None
13	F	55	Duodenum	TM	IV	B obstruction
14	F	65	Rectum	TM	II	None
15	F	51	A. colon, ileocecum	U	III	None
16	M	26	D. colon, t. colon, a. colon, ileocecum	U	II	None
17	M	21	S. colon, t. colon, a. g colon, terminal ileum	U	II	None
18	M	38	S. colon	U	III	None
19	M	15	S. colon	U	III	None
20	M	35	Rectum, s. colon, d. colon, t. colon, a. colon	U	IV	None
21	M	32	A.colon, ileocecum, terminal ileum, duodenum	U	IV	None
22	M	32	Ileocecum	U	I	None
23	F	41	A. colon, rectum	TM	III	B obstruction
24	M	33	T. colon, a. Colon	U	II	None
25	M	31	Ileocecum	U	II	None

TM=tumor mass; U=ulcer; M=male; F=female; A=ascending; D=descending; T=transverse; S=sigmoid; B=bowel.

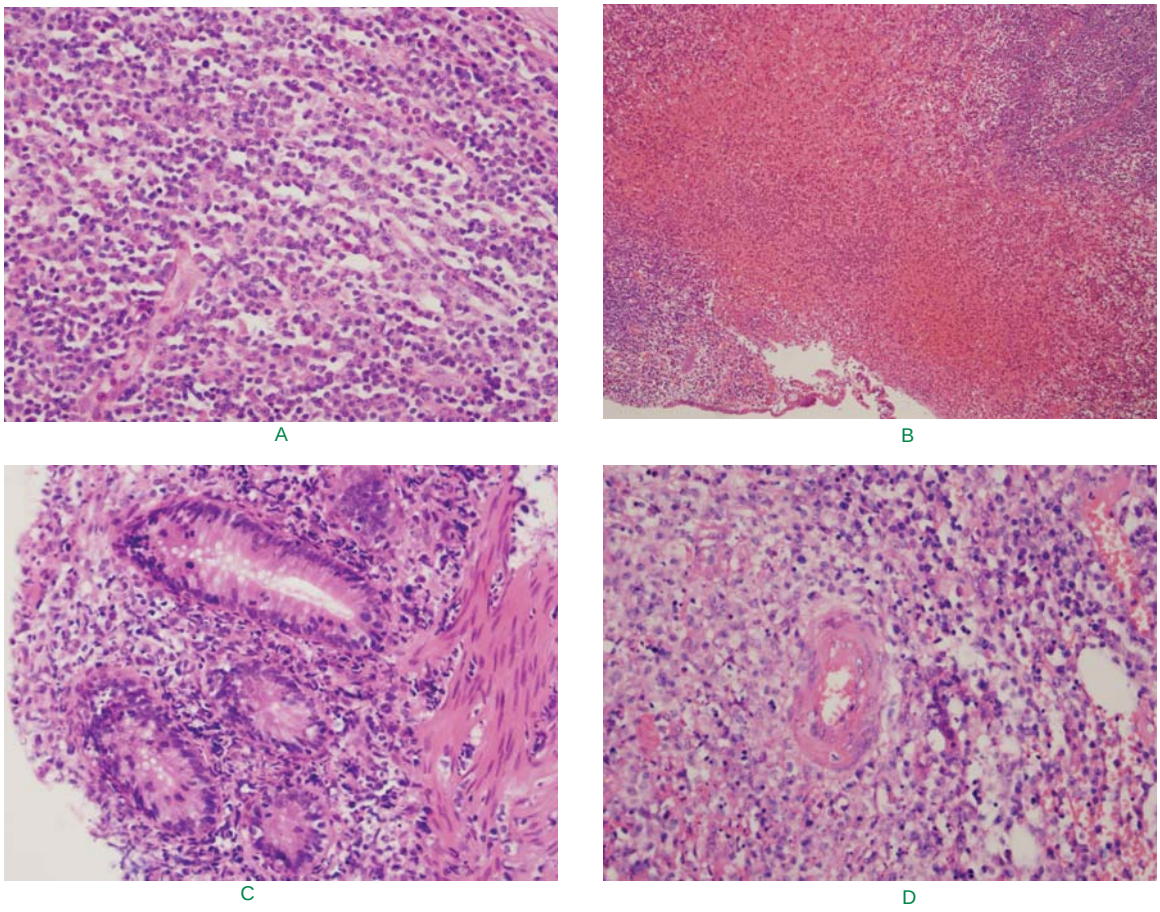

Figure 2. Histological findings of colonic NK/T cell lymphoma (H&E). Medium-sized to large pleomorphic ALCs disseminated in the submucosa **(A)**. Massive necrosis **(B)**, LEL **(C)**, and angiocentric infiltration **(D)** were characteristic. A, C, and D, 400×; B, 100×.

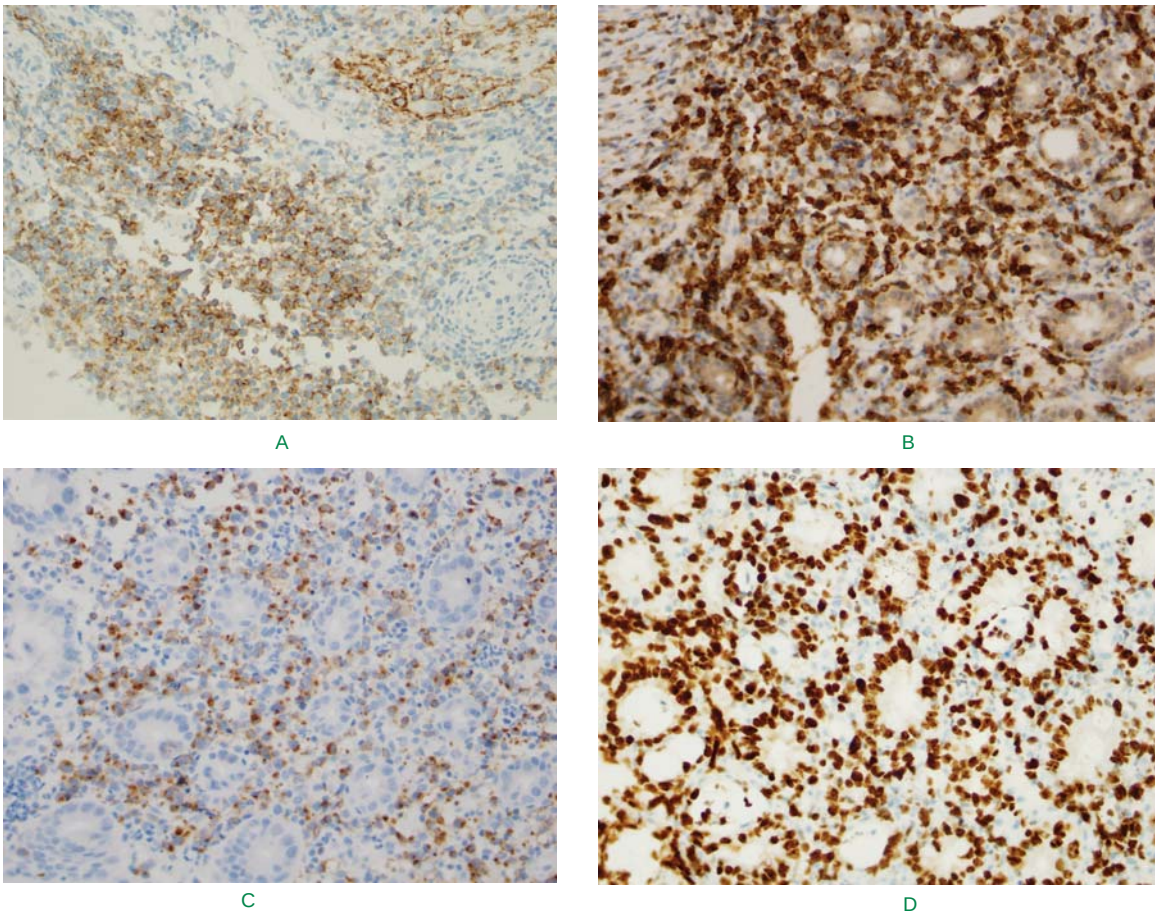

Figure 3. Immunohistochemical staining of the tumor. Neoplastic cells strongly expressed CD56 **(A)**, CD3ε **(B)**, granzyme B **(C)**, and Ki 67 **(D)**. A, B, C, and D, 400×.

Immunohistochemistry

The ALCs in 21 of 25 cases (84%) expressed CD56 (Figure 3A); 15 of 17 cases (88.2%) expressed CD3ε (Figure 3B); and 18 of 20 (90%) expressed granzyme B (Figure 3C). Out of 14 cases, 12 (85.7%) highly expressed Ki67, with the positive percentage ranging from 50% to 80% (Figure 3D). None of the cases expressed CD20.

In situ *hybridization*

In situ hybridization indicated that 16 of 19 cases (84.2%) were positive for EBER.

TCR γ gene rearrangement

The TCR γ gene rearrangement was investigated in 9 of 25 cases. Only one case revealed monoclonal TCR γ gene rearrangement with a CD3, CD56, granzyme B, and EBER positive immunophenotype.

Diagnostic information

Clinical stage

At diagnosis, 3 of 25 cases were in Stage IE, 6 in Stage IIE, 7 in Stage IIIE, and 9 in Stage IVE. Out of 25, 16 (64%) were either Stage IIIE or Stage IVE.

Difficulty of diagnosis

Early diagnosis of primary intestinal NK/T cell lymphoma is difficult because the lymphoma may mimic intestinal tuberculosis (ITB) or Crohn's disease (CD) in some cases.

In this study, 3 cases presented as follows. The first patient had clinically suspected malignant lymphoma on the basis of segmental irregular ulcers from the ileocecum to the descending colon; however, the histopathology presented no evidence of a malignant lymphoma. Subtotal colon resection was then performed and he was diagnosed with CD by its typical histological features. Next the patient received anti-inflammatory and immunosuppressive therapies, but he underwent multiple fever relapses. The second patient received an appendectomy because of right lower abdominal pain and was histologically diagnosed with appendicitis. He had numerous fevers post-operatively. The colonoscopy showed multifocal transverse ulcers in the colon. He received diagnostic anti-tuberculosis medication at first, and later anti-inflammatory therapies as a diagnosis of colonic CD. His symptoms remained unchanged and were followed by recurrences of hyperpyrexia. We had a clinical suspicion of intestinal malignant lymphomas, although we failed to confirm it histologically. During the months of their treatments and surveillance periods, the above two patients were finally diagnosed with primary colonic NK/T cell lymphomas through endoscopic biopsy specimens. The last case was clinically suspected of having tuberculous peritonitis due to the symptoms of fever, abdominal pain, ascites, and encapsulated hydrops in the abdominal cavity, however anti-tuberculosis medication seemed to be ineffective. He received an exploratory laparotomy, which revealed primary colonic NK/T cell lymphoma complicated by colonic perforation.

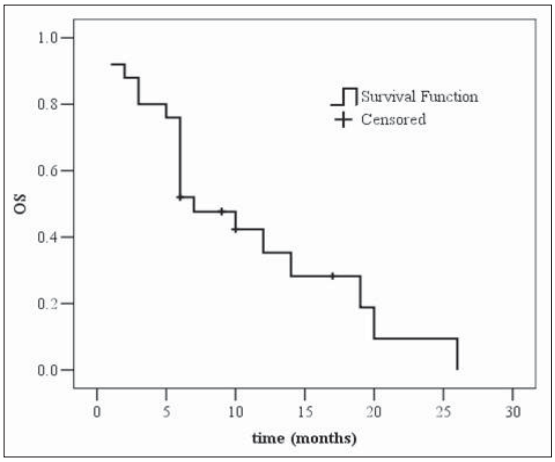

Figure 4A. Survival of 25 primary intestinal NK/T cell lymphoma cases.

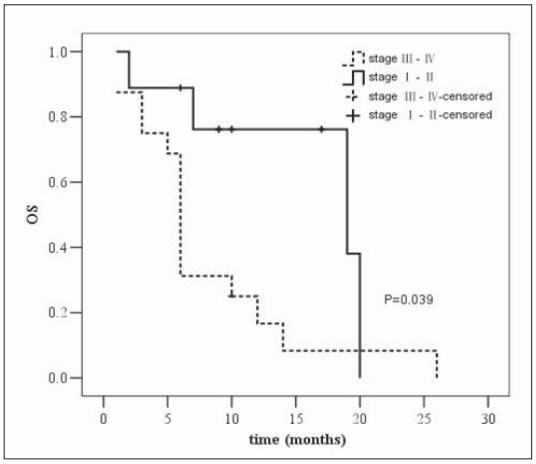

Figure 4B. Survival according to Ann Arbor staging in 25 primary intestinal NK/T cell lymphoma patients.

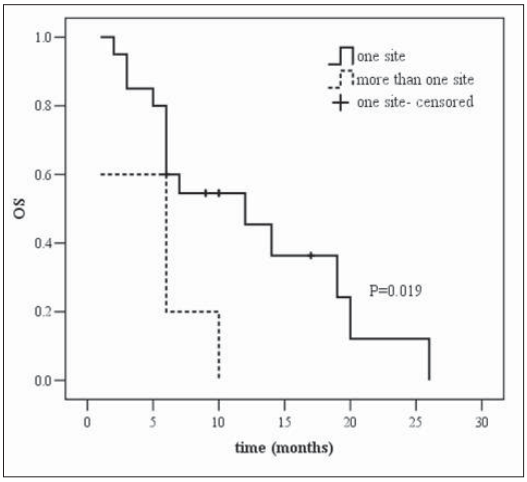

Figure 4C. Survival according to extranodal site involvement in 25 primary intestinal NK/T cell lymphoma cases.

Misdiagnosis

In this study, 5 of 25 cases (20%) were misdiagnosed as ulcerative colitis (UC), CD, ITB, peptic ulcer, and duodenal carcinoma.

Follow up data

Treatment information was obtained for 22 of 25 patients. Of these, 15 of the 22 cases received bowel resection, in which 3 underwent adjuvant chemotherapy (CHOP protocol) combined with radiotherapy; 7 received adjuvant chemotherapy (CHOP protocol); and 5 only had surgery. A total of 11 of 15 cases received palliative surgery, while 4 underwent curative surgery. Out of 22 cases, 3 underwent chemotherapy (CHOP protocol) alone and 4 abandoned their treatments.

The two cases with the longest survival time (20 and 26 months) and the one alive were all in Stage IE at diagnosis. The cases were morphologically featured by small ALCs infiltrates without angiocentric invasion. The two cases with longer survival received curative bowel resection combined with chemotherapy and radiotherapy and the one alive underwent curative surgery combined with adjuvant chemotherapy.

Survival analysis

After a median follow-up of 7 months (range: 1 to 26 months), 3 of 25 patients were alive at the last follow-up and 3 cases became lost to follow-up. There were 19 out of 22 patients who died of progressive disease with a median survival of 7 months. A Kaplan Meier survival curve showed that the one-year OS of 25 primary intestinal NK/T cell lymphoma cases was 35.3% (Figure 4A).

Survival curves were plotted for gender, age, PS score, Ann Arbor staging, number of extranodal site involvement, LDH, and IPI score. Ann Arbor stage IIIE/IVE and more than one extranodal site of disease significantly shortened the OS of patients with primary intestinal NK/T cell lymphoma (one-year OS 17% vs. 76%, P = 0.039, Ann Arbor stage IIIE/IVE, Figure 4B; and one-year OS 0% vs. 46%, P = 0.019 for more than one extranodal site of disease, Figure 4C). Gender, age, PS score, LDH, and IPI score did not significantly affect OS (Table 1).

Discussion

Intestinal T cell and NK cell lymphomas (ITNKLs) account for 5.2% to 14.7% of primary gastrointestinal malignant lymphomas.[6–8] Primary ITNKLs include enteropathy-associated T

cell lymphoma (EATL), anaplastic large cell lymphoma, nasal type NK/T cell lymphoma, and peripheral T cell lymphoma, unspecified.[9] Nasal type NK/T cell lymphoma is prevalent in Asia and Central and South America,[3,10–12] and most commonly favors young people with a poor prognosis,[13–16] while the predominant EATL observed in Northern Europe mainly occurs in middle and old age.[17–19]

The clinical presentations of primary intestinal NK/T cell lymphomas in our patients were consistent with those reported in prior studies.[5,15,16] Nonspecific symptoms can be separated into those secondary to tumor formation (abdominal pain, diarrhea, and intestinal obstruction), tissue destruction (bowel perforation, peritonitis, and gut hemorrhea) and into generalized symptoms (fever and weight loss). Endoscopically, intestinal NK/T cell lymphomas of our patients most commonly showed focal, multifocal, or diffuse irregular ulcers that most frequently occurred in the ascending colon, while the ITNKLs developed in Europe were mainly localized to the jejunum.[8,18]

Due to its diverse clinical and endoscopic findings, primary intestinal NK/T cell lymphoma is frequently difficult to distinguish from infectious, inflammatory, granulomatous, and neoplastic disorders. The histological diagnosis of primary NK/T cell lymphoma of the intestine may be confused with an inflammatory or infectious process. There are a few reasons for this. First, the florid inflammatory infiltrates can be similar to those of inflammatory bowel disease (IBD) or infectious colitis and may obscure the relatively small number of tumor cells present in some cases. Second, it is difficult to distinguish the predominant small ALCs from normal reactive lymphocytes. Finally, the early presence of ALCs are usually clustered deep in the submucosa, subsequently expanding further to the muscularis propria, or even break through the serous membrane, which makes it difficult to obtain such deep minute tumors using forceps. Therefore, clinically suspected malignant lymphoma with negative histological evidence should not be given up completely. Repeated deep biopsies are strongly recommended during the follow-up and treatment period, and if necessary an exploratory laparotomy can be determined in time for early diagnosis. Histological suspicion of malignant lymphoma depends on atypical lymphoid infiltration, especially when routine medications seem to be ineffective or clinical courses became aggressive.

ITNKLs, especially EATL and primary intestinal NK/T cell lymphoma, differ in morphology and immunophenotype.[4,20,21] EATL is an intestinal tumor of intraepithelial T lymphocytes. The adjacent small intestinal mucosa shows villous atrophy with crypt hyperplasia. Most commonly, the tumor cells are relatively monotonous medium to large sized cells with round or angulated vesicular nuclei, prominent nucleoli, and a moderate to abundant pale-staining cytoplasm. The tumor cells are CD3+, CD7+, and CD103+, and contain cytotoxic granule associated proteins. The intraepithelial lymphocytes in the adjacent mucosa share the identical immunophenotype. Nasal type NK/T cell lymphoma is designated "NK/T" (instead of "NK"), because while most cases appear to be genuine NK cell neoplasms, some cases show a cytotoxic T cell phenotype. It is a predominantly extranodal lymphoma characterized by vascular damage and destruction, prominent necrosis, and a cytotoxic phenotype. In most cases, the lymphoma is composed of medium-sized cells or a mixture of small and large cells. The cells often have irregularly folded nuclei and inconspicuous or small nucleoli. The cytoplasm is moderate in amount and often a pale to clear color. Mitotic figures are easily found. The most typical immunophenotype of extranodal NK/T cell lymphoma is CD2+, CD56+ and cytoplasmic CD3ε+. Cytotoxic molecules, such as granzyme B, T cell intracellular antigen 1 (TIA-1) and perforin are positive.

The immunohistochemical results of the present series generally fall within the broad ranges reported in a previous study.[22] Although four cases in our report were negative for CD56, they were diagnosed with primary intestinal NK/T cell lymphomas. Because these patients were positive for CD3ε, EBER, and granzyme B, they shared the similarities of clinical and histological features with those who were positive for CD56.[4] In accordance with previous studies,[22,23] 85.7% of the cases in our study highly expressed Ki67, indicating that high Ki67 expression had a significant correlation with poor prognosis. It has been reported that there is a high incidence of EBV infection in nasal NK/T cell lymphomas in Asia, with positive frequencies of EBER ranging from 76% to 97.6%.[5,24] Another study stated that EBV negative patients had a rather longer survival than EBV positive cases, indicating that EBV infection may be an independent negative prognostic factor in NK/T cell lymphomas.[14] TCR γ gene rearrangement investigation also plays an important role in the diagnosis of NK/T cell lymphoma. The NK cell presents a germ line TCR γ gene, while the cytotoxic T cell manifests monoclonal rearrangement of the TCR γ gene. In our series, 1 of 9 cases revealed clonal rearrangement of the TCR γ gene and a CD56, CD3, granzyme B, and EBER positive immunophenotype. This suggests a NK-like cytotoxic T cell origin, whereas the other 8 cases were of true NK cell origin. The above immunological markers and TCR γ gene detection are key evidence in the differential diagnosis of T cell and NK/T cell lymphomas.

The follow-up data in our report indicated that primary intestinal NK/T cell lymphoma had a poor prognosis with a median survival of 7 months. The early diagnosis of this neoplasm is difficult. There were 64% of our patients who were in advanced stages at diagnosis, and the daily living abilities of 60% cases were affected by disease progression before treatment. Misdiagnosis occurred in 20% of cases, mostly as IBD and ITB. Two patients initially suspected to have malignant lymphoma arrived at their final diagnosis after long periods of monitoring, which may suggest a potential correlation between intestinal malignant lymphoma and IBD.

Survival analysis of the present series suggested that stage IIIE or IVE and more than one extranodal site of disease are significant unfavorable prognostic factors, which is consistent with previous studies.[25] Unlike results in other reports, age, sex, LDH, and PS score failed to predict the survival outcome of our cases, which may warrant further study on accumulative primary intestinal NK/T cell lymphoma cases. The prognostic impact of IPI remains controversial in NK/T cell lymphoma.[26–28] In our primary intestinal NK/T cell lymphoma series, IPI failed to predict the outcome. When using IPI, 80% of our patients were categorized as either a low risk group or low-intermediate risk group; however, the one-year OS was only 35.3%, which suggests that there may be other prognostic factors independent of IPI in primary intestinal NK/T cell lymphoma. Ko[14] and Tang[25] have suggested that the morphology of tumor cells and angiocentric invasion might be associated with the outcome of NK/T cell lymphoma. In our study, two cases with longer survival and one that survived were all in Stage IE at diagnosis and the morphology of their lymphomas featured small ALCs infiltrates without angiocentric invasion. These two patients received curative surgery combined with radiotherapy and/or chemotherapy. So we expect early diagnosis and combined therapy to improve poor prognosis.

References

1. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: Distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol*. 1998; **9:** 717 – 720.
2. Chuang SS, Lin CN, Li CY. Malignant lymphoma in southern Taiwan according to the revised European-American classification of lymphoid neoplasms. *Cancer*. 2000; **89:** 1586 – 1592.
3. Lymphoma Study Group of Japanese Pathologists. The World Health Organization classification of malignant lymphomas in Japan: Incidence of recently recognized entities. *Pathol Int*. 2000; **50:** 696 – 702.
4. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008: 285 – 288.
5. Zhang WY, Li GD, Liu WP, Ouyang Q, Ren XC, Li FY, et al. Features of intestinal T-cell lymphomas in Chinese population without evidence of celiac disease and their close association with Epstein–Barr virus infection. *Chin Med J (Engl)*. 2005; **118:** 1542 – 1548.
6. Nakamura S, Matsumoto T, Iida M, Yao T, Tsuneyoshi M. Primary gastrointestinal lymphoma in Japan: A clinicopathologic analysis of 455 patients with special reference to its time trends. *Cancer*. 2003; **97:** 2462 – 2473.
7. Kohno S, Ohshima K, Yoneda S, Kodama T, Shirakusa T, Kikuchi M. Clinicopathological analysis of 143 primary malignant lymphoma in the small and large intestines based on the new WHO classification. *Histopathology*. 2003; **43:** 135 – 143.
8. Chott A, Dragoscic B, Radaszkiewicz T. Peripheral T-cell lymphoma of the intestine. *Am J Pathol*. 1992; **141:** 1361 – 1371.
9. Feller AC, Diebold J. Extranodal lymphoma. In: Feller AC, Diebold J, eds. *Histopathology of Nodal and Extranodal Non-Hodgkin's Lymphomas*. Berlin; Germany: Springer; 2004: 205 – 213.
10. Au WY, Ma SY, Chim CS, Choy C, Loong F, Lie AK, et al. Clinicopathologic features and treatment outcome of mature T-cell and natural killer-cell lymphomas diagnosed according to the World Health Organization classification scheme: a single center experience of 10 years. *Ann Oncol*. 2005; **16:** 206 – 214.
11. Chan JK. Natural killer cell neoplasms. *Anat Pathol*. 1998; **3:** 77 – 145.
12. Quintanilla-Martinez L, Franklin JL, Guerrero I, Krenacs L, Naresh KN, Rama-Rao C, et al. Histological and immunophenotypic profile of nasal NK/T cell lymphomas from Peru: high prevalence of p53 overexpression. *Hum Pathol*. 1999; **30:** 849 – 855.
13. Suzuki R. leukemia and lymphoma of nature killer cells. *J Clin Exp Hematopathol*. 2005; **45:** 51 – 70.
14. Ko YH, Cho EY, Kim JE, Lee SS, Huh JR, Chang HK, et al. NK and NK-like T-cell lymphoma in extranasal sites: A comparative clinicopathological study according to site and EBV status. *Histopathology*. 2004; **44:** 480 – 489.
15. Kim HS, Lee DK, Baik SK, Kwon SO, Cho MY, Ko YH. Primary CD56+ T/NK cell lymphoma of the colon. *J Gastroenterol*. 2002; **37:** 939 – 946.
16. Tung CL, Hsieh PP, Chang JH, Chang JH, Chen RS, Chen YJ, et al. Intestinal T-cell and natural killer-cell lymphomas in Taiwan with special emphasis on 2 distinct cellular types: Natural killer-like cytotoxic T cell and true natural killer cell. *Human Pathology*. 2008; **39:** 1018 – 1025.
17. Domizio P, Owen RA, Sheperd NA, Talbot IC, Norton AJ. Primary lymphoma of the small intestine. A clinicopathological study of 119 cases. *Am J Surg Pathol*. 1993; **17:** 429 – 442.
18. Chott A, Haedicke W, Mosberger I, Fodinger M, Winkler K, Mannhalter C, et al. Most CD56+ intestinal lymphomas are CD8+CD5-T-cell lymphomas of monomorphic small to medium size histology. *Am J Pathol*. 1998; **153:** 1483 – 1490.
19. Daum S, Foss HD, Anagnostopoulos I, Dederke B, Demel G, Araujo I, et al. Expression of cytotoxic molecules in intestinal T-cell lymphomas. The German Study Group on Intestinal Non-Hodgkin Lymphoma. *J Pathol*. 1997; **182:** 311 – 317.
20. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System*. Hamilton SR, Aaltonen LA eds. Lyon: IARC Press; 2000: 87 – 89.
21. Fenoglio-Preiser CM, Noffsinger AE, Stemmermann GN, Lantz PE, Isaacson PG. *Gastrointestinal Pathology: An Atlas and Text*. 3rd ed. Philadelphia (America): Lippincott, Williams and Wilkins; 2007: 1188 – 1196.
22. Schwartz EJ, Molina Kirsch H, Zhao S, Marinelli RJ, Warnke RA, Natkunam Y. Immunohistochemical characterization of nasal-type extranodal NK/T-cell lymphoma using a tissue microarray: An analysis of 84 cases. *Am J Clin Pathol*. 2008; **130:** 343 – 351.
23. Kim SJ, Kim BS, Choi CW, Choi J, Kim I, Lee YH, et al. Ki67 expression is predictive of prognosis in patients with stage I/ II extranodal NK/ T cell lymphoma, nasal type. *Ann Oncol*. 2007; **18:** 1382 – 1387.
24. Ng SB, Lai KW, Murugaya S, Lee KM, Loong SL, Fook-Chong S, et al. Nasal-type extranodal natural killer/T-cell lymphomas: a clinicopathologic and genotypic study of 42 cases in Singapore. *Mod Pathol*. 2004; **17:** 1097 – 1107.
25. Tang QL, Liu WP, LI GD, Xu H, Yang F, Chen DZ. Clinicopathologic features and prognostic factors of nasal and nasal-type NK/ T lymphoma in south west part of China (in Chinese with English abstract). *Tumor*. 2003; **23:** 411 – 413.
26. Chim CS, Ma SY, Au WY, Choy C, Lie AK, Liang R, et al. Primary nasal natural killer cell lymphoma: Long-term treatment outcome and relationship with the International Prognostic Index. *Blood*. 2004; **103:** 216 – 221.
27. Cheung MM, Chan J, Lai W, Ngan RK, Foo WW. Early stage nasal NK/T-cell lymphoma: Clinical outcome, prognostic factors, and the effect of treatment modality. *Int J Radiat Oncol Biol Phys*. 2002; **54:** 182 – 190.
28. You JY, Chi KH, Yang MH, Chen CC, Ho CH, Chau WK, et al. Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: A single institute survey in Taiwan. *Ann Oncol*. 2004; **15:** 618 – 625.