Clinicopathologic Analysis of 12 Cases of Cutaneous Extranodal NK/T-Cell Lymphoma

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Research Article

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Abstract

Background To investigate the clinical and pathological features of cutaneous extranodal natural killer/T-cell lymphoma (CENKTL).

Methods Clinical data of 12 patients with CENKTL who were admitted to the Affiliated Hospital of Xuzhou Medical University between February 2013 and February 2021 were retrospectively analyzed, and the patients were followed up.

Results The patients included 10 men and two women, and their ages ranged from 19 to 92 years. The lesion distribution was as follows: the extremities, six cases; the nose and face, two cases; the trunk, three cases; and disseminated disease, one case. The patients' clinical presentation consisted of erythema, papules, nodules, and ulceration. Histopathological examinations showed abnormal proliferation of lymphocytes that had infiltrated the dermis and subcutaneous region. The tumor tissue showed central growth of blood vessels, vascular occlusion, and coagulation necrosis. The tumor cells were mainly of medium size, and nuclear divisions were common. In situ hybridization revealed that Nine patients were positive for Epstein–Barr virus-coding RNA (EBER). Immunohistochemistry showed that the tumor cells were positive for CD3ε (11 patients), CD56 (11 patients), TIA-1 (seven patients), and CD20 (three patients). Eleven patients were positive for Ki-67 with values of 30%-90%. Seven of the 12 patients died, and one patient was lost to follow up. The time from onset to diagnosis was 1–42 months.

Conclusion CENKTL is highly invasive, with a short survival period and poor prognosis, and its diagnosis depends on histopathology, immunohistochemistry, and EBER in situ hybridization results.

1. Introduction

Extranodal NK/T-cell lymphoma (ENKTL) is a rare and highly malignant type of non-Hodgkin's lymphoma, which could have features such as vascular destruction and marked tissue necrosis. It is closely related to infection with the Epstein–Barr virus (EBV) [1]. ENKTL exhibits a predilection to develop *in* the upper aerodigestive tract and most commonly occurs *in* the nasal cavity, nasopharynx, and oral cavity. However, it can also develop in the skin, gastrointestinal tract, testis, lungs, and central nervous system. The skin is the most common site of extranasal ENKTL development, but it is extremely rare. Compared to extracutaneous lesions such as those that develop in the nasopharynx, skin lesions are easier to detect and can be the most direct clue for the discovery of ENKTL. According to the primary site of involvement, cutaneous ENKTL can be divided into two subgroups: primary cutaneous ENKTL (PCENKTL) and ENKTL with secondary spread to the skin (SCENKTL), and the former is more common than the latter [2]. Although extranasal ENKTL has been widely evaluated, there is only limited data about clinicopathological characteristics or prognosis of patients with cutaneous ENKTL. Therefore, in this study, we reviewed 12 cases of cutaneous ENKTL to better characterize this rare histopathologic variant of ENKTL.

2. Materials And Methods

This study obtained approval from the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University, and the requirement for informed consent was waived. The data of 12 patients with CENKTL who were treated at the Affiliated Hospital of Xuzhou Medical University between February 2013 and February 2021 were collected. CENKTL was diagnosed based on the findings of a skin lesion biopsy. The diagnostic criteria were based on the World Health Organization's (2016) classification of lymphoid neoplasms [3]. Staging for all patients was performed according to the Ann Arbor staging system. Overall survival (OS) was defined as the time between the date of disease diagnosis and the patient's death from any disease, the time of the last follow-up, or the end of the observation period.

The clinical and pathological data collected included the following: clinical manifestations; laboratory examination and histopathology findings; immunophenotype; type of treatment; and last follow-up, treatment response, progression, and survival data(Table 1-2). Then, relevant literature was reviewed to summarize the clinical features, histopathological characteristics, and therapeutic strategies for CENKTL.

3. Results

3.1 Clinical data

The age range of the 12 patients (10 men and 2 women; male-to-female ratio, 5:1) at diagnosis was 19 to 92 years. Eight (66.7%) patients were older than 60 years, and the median patient age was 64.5 years. Based on the primary site of involvement, eight (66.7%) patients had PCENKTL and four (33.3%) patients had nasal ENKTL with cutaneous involvement. Five (41.7%) of the patients presented with localized cutaneous lesions, whereas seven (58.3%) had multiple cutaneous lesions. Localized cutaneous lesions were more common in PCENKTL compared to that in SCENKTL; however, the difference was not significant.

Cutaneous lesions were predominantly distributed throughout the extremities (6) and trunk (3), but most especially the lower extremities (6). In two patients, they were located on the nose and face, whereas one patient showed multifocal cutaneous involvement. The clinical presentation consisted of erythema (25%), multiple nodules (33.3%), and masses (16.7%) (Fig. 1A-B); furthermore, ulceration was noted in seven patients (58.3%). Eight (66.6%) patients presented with B symptoms: fever, four (33.3%) patients; night sweats, three (25%) patients; and weight loss, one (8.3%) patient.

3.2 Laboratory inspection

Lactate dehydrogenase (LDH) levels were elevated in four patients (33.3%). Furthermore, simple leukopenia was observed in two patients, and decreased *white blood* cell, platelet, *and* red blood cell counts were noted in one patient. Of these patients, six were administrated bone marrow cytology, and among these six, no lymphoma cells were found. Circulating EBV DNA was tested in only 5 patients and all were positive, 4 of which had elevated β2 microglobulin. The PET/CT was carried out in 6 cases, and all helped identify malignancy, including two cases with nasal-paranasal cavity involvement, one case with lung involvement, and lymph node involvement was noted in five patients. According to the Ann Arbor staging system, two patients had stage I/II disease and 10 had stage III/IV disease. Most patients were classified as the high-risk group.

3.3 Histopathological features

All patients with CENKTL underwent a pathological examination of the skin
lesions. Histopathological examinations showed abnormal proliferation of lymphocytes that had infiltrated the dermis and subcutaneous region. Tumor tissue showed central growth of blood vessels, vascular occlusion, and coagulation necrosis. The tumor cells were mainly medium-sized, and nuclear divisions were common (Fig. 2A-B).

3.4 Immunohistochemistry and EBV status

Immunohistochemistry showed that the tumor cells were positive for CD2 (7/7, 100%), CD3ε (11/11, 100%) (Fig. 2C), and CD56 (11/11) (Fig. 2D); cytotoxic proteins such as TIA-1 (7/7, 100%), perforin (4/7, 33.3%), and granzyme B (5/5, 100%); CD20 (3/11, 27.3%) (Fig. 2E-F), and PAX-5 (1/6, 16.7%). The positivity of the proliferating nuclear antigen (Ki-67) (11/11, 100%) was 30%-90% (Fig. 2G). In situ hybridization showed positive nuclei of EBV-coding RNA (EBER) (9/9,100%) (Fig. 2H).

3.5 Treatment response and survival

In all, two (16.7%) patients received chemotherapy combined with radiotherapy; three (25.0%) patients were treated with only chemotherapy, and one (8.3%) patient was treated with radiotherapy. One (8.3%) advanced patient underwent high-dose *chemotherapy* and *autologous stem cell* transplantation (ASCT), and 4 (33.3%) individuals declined treatment altogether. The chemotherapy regimens were CHOP (cyclophosphamide + doxorubicin, epirubicin, or pirarubicin + vincristine + prednisone, 1 case), CHOP + L (L-asparaginase, 3 cases), and modified SMILE (ifosfamide + dexamethasone + mesna + etoposide + pegaspargase, 2 cases). Radiotherapy was performed with 50–*55* Gy, and the irradiation field for radiation therapy with X-rays needed to be expanded.

Six patients died from disease progression and one patient of cardiovascular disease. *Of the seven patients who died, three and four patients had* single and multiple lesions, respectively. Seven died in 1 month to 24 months, with a median of 10 months. Besides, four patients survived with or without disease, and one patient with PCENKTL was lost to follow-up. Three patients with PCENKTL are currently alive, while only one patient with secondary skin lesions is alive at present. Four were alive, with 3 being disease-free at 3 months, 12 months and 42 months, respectively, and 1 with relapse at 1 year. The median overall survival (OS) of Nasal ENKTL with secondary spread to the skin was 32 months from the first diagnosis, and 11 months from the presentation of a cutaneous lesion. When all patients were combined into a single cohort, the 2-year OS was 27.3% and the median OS was 10.0 months (range : 1 to 42 months).

4. Discussion

ENKTL originates from mature T and NK-cell lymphoma, which is rare, and regional and ethnic differences in the disease have been noted. It has been rarely reported in North American and European countries but is common in East Asian and South American countries, especially China [4], accounting for 15% to 30% of all lymphomas in China. However, regardless of whether the involvement of the skin is the primary or secondary manifestation of ENKTL, cutaneous ENKTL is extremely rare and has a poor prognosis [5].

Cutaneous ENKTL is more frequent in male individuals than in female individuals, and occurs frequently in middle-aged adults. In this study, 83.3% of the patients were men, and the male-to-female patient ratio was 5:1, which may be attributed to the limited size of the sample. The median age of the patients was 64.5 years, and 66.7% of the patients were older than 60 years, indicating a slightly higher proportion of elderly individuals in comparison with previous studies. In recent years, the published literature on cutaneous ENKTL is mainly focused on cases of primary cutaneous ENKTL, mostly in the form of case reports or reported in small series, while reports of nasal ENKTL with cutaneous involvement are even rarer.

In this study, among all subsets of cutaneous ENKTL, primary cutaneous ENKTL was the most common. All forms of nasal ENKTL with cutaneous involvement present within 2 years after the initial diagnosis of nasal ENKTL [6], while the mean time in our group was 15 months (range : 2 to 30 months). Nasal ENKTL with secondary spread to the skin was more likely than primary cutaneous ENKTL to present with generalized skin lesions [7]. The distribution of cutaneous ENKTL in the extremities was as high as 50.0%, followed by the trunk or head and neck. In this study, the clinical macroscopic findings of cutaneous ENKTL were characterized by erythema, papules, subcutaneous nodules, and ulceration, which was similar with the previous reports by Liang et al [5]. In all such patients, lesions were more common in the lower extremities, which may be related to T-cell homing [8]. Furthermore, the cutaneous lesions of the lower extremities were more likely to progress to ulceration. The causes of ulceration formation are consistent with the characteristics of tumor cells destroying blood vessels and secondary ischemic necrosis in histopathology. These groups of cutaneous ENKTL showed no remarkable differences in terms of the clinical features of the cutaneous lesions, except in terms of stage.

More than half of the patients with primary cutaneous ENKTL developed extracutaneous lesions several months after the appearance of skin lesions. However, in this study, involvement of the lymph nodes, nasal cavity, or sinus and lungs was observed by PET/CT in patients showing skin lesions, while bone marrow involvement was rare. Therefore, a full diagnostic workup is required when skin lesions are found, and attention should be paid to lesions outside the skin, which have a certain influence on disease evaluation and prognosis judgment. Moreover, the results of this study showed B symptoms in approximately 66.6% of the patients, which can occur at any time in the disease course. Many studies have shown that B symptoms are a poor prognostic factor for ENKTL [9-10].

In this group, histopathological examinations typically showed polymorphous diffuse and angiocentric lymphoid infiltrate involving dermis and subcutaneous region, in association with angiodestruction and coagulative necrosis. The tumor cells showed irregular folded nuclei. In addition, cells size ranges from small to large, but most patients mainly showed medium-sized cells or a mixture with many types of cells. Histopathological assessments are of great significance to the diagnosis of ENKTL, but they are difficult to evaluate. Besides, the clinical manifestations of cutaneous ENKTL at an early stage are not typical, almost all patients were misdiagnosed with inflflammatory lesions at onset, which can easily lead to missed diagnosis and misdiagnosis. Therefore, detection based on immunohistochemistry and EBER in situ hybridization detection should be performed at an early stage. If necessary, *multiple* biopsies are recommended to improve accurate diagnosis of cutaneous ENKTL.

Immunohistochemical findings for this disease often show the neoplastic cells are positive for CD2, CD3ε, cytotoxic protein (TIA-1, perforin, and GranB) and CD56, frequently negative for other T-lineage markers and B-cell antigen (CD20). CD56 is a marker for NK cells, expressed in a subset of CD4 and CD8 cells, and is positive in 74% to 76% of cases of ENKTL [11]. In accordance with published literature, there are no significant differences in the clinicopathological features between CD56 positive and CD56 negative cases [12]. Therefore, for rare CD56 negative cases, the detection of EBV and expression of cytotoxic proteins are required for diagnosis. The high expression levels of Ki-67 are related to the volume of the primary lesion. Large tumors (volume >10 cm^3) may have a higher ability to show tumor cell proliferation, and their prognosis is significantly worse than that in the low-expression group, which can be used as one of the prognostic indicators of ENKTL.

CD20 is a specific marker of B-cell lymphoma that serves as a target for therapeutic monoclonal antibodies for the treatment of B-cell lymphomas and leukemias. CD20 expression in T-cell lymphoma has been gradually reported in recent years. However, abnormal expression of CD20 in ENKTL is very rare, mainly occurs in extranasal ENKTL, and is associated with an advanced and poor prognosis. Abnormal expression of CD20 in ENKTL suggests a high proliferation rate, similar to the high expression level of Ki-67 in tumor cells [13]. But now, the cutaneous lesions of three patients in this group were CD20-positive, as well as high expression levels of Ki-67 (60%-90%), and they were all in advanced stage, indicating a worse prognosis. It is difficult to distinguish abnormal expression of CD20 in ENKTL from B-cell lymphoma with exceptional expression of T cell markers. 3 cases of CD20 abnormal expression of ENKTCL patients expressed multiple NK/T cell markers, and B cell markers only expressed CD20. On the contrary, in addition to weakly expressing PAX-5, B-cell lymphoma cells with exceptional expression of T-cell markers showed diffuse expression of CD20, CD79a, CD19, BOB-1 and other B-cell markers. In short, CD20 increases the difficulty of diagnosis, so diagnosis requires a combination of multiple tests pathology, immunohistochemistry, EBER, and gene rearrangement.

Interestingly, One patient in this group showed CD20-positive primary nasal lesions. With the progression and spread of the disease, lesions of the penis and scrotum showed weak positivity for CD20. Finally, cutaneous lesions showed a CD20-negative status. In contrast, one case of primary nasal ENKTCL showed acquisition of CD20 expression in cutaneous relapse. Immunohistochemistry of the primary and relapsed lesions in these two cases of ENKTL with secondary spread to the skin showed only discordant CD20 expression, which may be due to tumor transformation of

progenitor cell subsets that co-express CD20 and NK-cell markers, or the neoplastic process after neoplastic transformation, with the latter seeming more plausible [10]. Nevertheless, the underlying mechanism remains to be further studied.

EBER are EBV-encoded small mRNA expressed at all stages of EBV infection. All nine patients were EBER-positive, further indicating that EBV infection was closely related to the incidence of ENKTL. Moreover, there was no difference in histopathology and immunophenotypic changes in nasal and extranasal ENKTL, but the detection rate of the former EBV was higher than that of the latter [14]. The pathogenesis of EBV tumors is different between elderly and young patients may be related to the immune degradation caused by aging [15]. However, EBV-negative results do not exclude the possibility of an ENKTL diagnosis. EBV-negative ENKTL is a rare subtype with limited available data. Previous studies have reported EBV-negative patients showed an inert clinical outcome and had a better prognosis than those with positive patients. But Nicolae et al [16] showed that EBV-negative patients was indistinguishable clinically and pathologically from positive patients, with a similar fulminant clinical course. By the way, measuring circulating EBV DNA can be used to determine a treatment algorithm and serve as an objective criteria for follow-up of their apeutic efficiency.

Currently, there is no consensus regarding the proper treatment strategy, and the main treatments for ENKTL patients are chemotherapy, radiotherapy, and chemotherapy combined with radiotherapy. For localized disease (I/II), radiotherapy alone has a good short-term effect, but the rate of late recurrence and metastasis is higher in patients receiving this treatment [17]. Combined therapy can be administered as simultaneous chemoradiotherapy or sequential chemoradiotherapy, both of which have good effects on the treatment of early ENKTL patients. However, patients with advanced stage (III/IV), relapse, and refractory disease mainly receive systemic chemotherapy alone, since the target lesions are extensive and may not be suitable for local radiotherapy. Avilés et al. [18] compared the prognosis of ENKTL patients treated with radiotherapy alone, chemotherapy alone and combined chemoradiotherapy, and found that complete response(CR), 5-year progression-free survival (PFS) and 5-year OS of combined chemoradiotherapy were all higher than those treated with radiotherapy alone or chemotherapy alone.

To date, there is no standard chemotherapeutic protocol for ENKTL. Conventional CHOP regimens (anthracycline-containing) was confirmed ineffective to ENKTL [19]. The present study found that chemotherapy regimens based on pegaspargase (PEG-ASP) or L-asparaginase (L-ASP) yielded promising results in the treatment of ENKTL. However, L-ASP has many adverse reactions, limiting its clinical application, while PEG-ASP can effectively preserve the original activity of L-ASP with few adverse reactions. PEG-ASP can be combined with gemcitabine and chidamide in chemotherapy, and in recent years, the latter has achieved significant efficacy in the treatment of ENKTL. The use of *radiotherapy and chemotherapy combined* with autologous hematopoietic stem cell transplantation (ASCT) has been demonstrated to improve treatment efficacy [20,21]. In this group, one patient with diffuse skin lesions received ASCT after complete remission of chemotherapy, and survived for 31 months without tumor recurrence, showing significant efficacy. However, the number of cases of HSCT for ENKTL are relatively rare, and its clinical efficacy remains to be further studied. In addition, some new therapeutic methods, such as biological targeted therapy and cellular immunotherapy, are still being explored to provide new therapeutic directions for ENKTL.

Primary cutaneous ENKTL has been reported to be less aggressive and to show a better prognosis than nasal ENKTL with cutaneous involvement, and patients with single lesions had lower mortality and better prognosis than those with multiple lesions, while the prognosis of primary cutaneous ENKTL with secondary nasal lesions was not significantly different from that of nasal ENKTL [7,22]. However, the mortality and prognosis of patients with localized and multiple cutaneous lesions in this group were slightly different from those in previous studies, which may be attributed

to the limited number of samples collected or the improvements associated with the current advanced treatment regimens.

Previous studies have shown that the median survival time ranges from 2 to 15 months for patients with cutaneous ENKTL in most series, and the estimated 5-year survival of 0% [23]. Jiang L et al [2] reported that the 3-year OS rates of cutaneous ENKTL were 73.9 % for patients who achieved complete response (CR) compared with 10.3 % for patients who did not. Takata K et al [24] found that the 5-year overall survival rate of primary cutaneous ENKTL was 25%. However, the prognosis of patients in this group was poor and the 2-year OS was only 27.3%, and we would continue to follow up the patients. On the other hand, untreated patients had a 75% mortality rate overall, while one 92-year-old untreated patient with local recurrence is still alive and has lived for 35 months. The exact cause is unclear, but it could be the microenvironment of senescent tissue is less capable of supporting rapid tumor growth [25].

In summary, cutaneous ENKTL is rare in clinical practice, and is characterized by high invasiveness and a poor response to chemotherapy. For cases in which clinical symptoms do not match the signs, patients show progressive aggravation, or long-term treatment is not curative, especially with B symptoms and lymph node enlargement, we should be highly alert to the possibility of this disease. Timely histopathological and immunohistochemical examinations, early diagnosis, and treatment can improve the prognosis of patients.

Declarations

Conflict of Interest: None.

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Competing Interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of the Affiliated Hospital of Xuzhou Medical University approved this study.

Informed consent: It is not necessary to obtain consent.

References

1. Somasundaram N, Lim JQ, Ong CK, er al. Pathogenesis and biomarkers of natural killer T cell lymphoma (NKTL). J Hematol Oncol. 2019;12:28.
2. Jiang L, Li P, Quan Q, et al. Cutaneous extranodal natural killer (NK) / T - cell lymphoma: A comprehensive clinical features and outcomes analysis of 71 cases. Leuk Res. 2020;88:106284.
3. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.
4. Liang X, Graham DK. Natural killer cell neoplasms. Cancer. 2008;112(7):1425-1436.

5. Kim TM, Lee SY, Jeon YK, et al. Clinical heterogeneity of extranodal NK/T-cell lymphoma, nasal type: a national survey of the Korean Cancer Study Group. Ann Oncol. 2008;19(8):1477-1484.
6. Qi SN, Li YX, Wang WH, et al. The extent of cutaneous lesions predicts outcome in extranodal nasal-type natural killer/T-cell lymphoma of the upper aerodigestive tract with secondary cutaneous involvement. Leuk Lymphoma. 2012;53(5):855-61.
7. Lee WJ, Jung JM, Won CH, et al. Cutaneous extranodal natural killer/T-cell lymphoma: a comparative clinicohistopathologic and survival outcome analysis of 45 cases according to the primary tumor site. J Am Acad Dermatol. 2014;70(6):1002-9.
8. Jalkanen S, Joensuu H, Söderström KO, et al. Lymphocyte homing and clinical behavior of non-Hodgkin's lymphoma. J Clin Invest. 1991;87:1835-1840.
9. Takata Katsuyoshi, Hong Min-Eui, Sitthinamsuwan Panitta, et al. Primary cutaneous NK/T-cell lymphoma, nasal type and CD56-positive peripheral T-cell lymphoma: a cellular lineage and clinicopathologic study of 60 patients from Asia. Am J Surg Pathol. 2015;39(1): 1-12.
10. Lee Jeeyun, Suh Cheolwon, Park Yeon Hee, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol. 2006; 24(4): 612-8.
11. Vainder C, Ho J, Swerdlow SH,et al. CD56- extranodal natural killer (NK)/T-cell lymphoma, nasal type presenting as skin ulcers in a white man. JAAD Case Rep. 2016;2(5):390-396.
12. Chan JK, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood. 1997;89(12):4501-13.
13. Huang Y, Chen S, Wei R, et al. CD20-positive extranodal NK/T cell lymphoma: clinicopathologic and prognostic features. Virchows Arch. 2020;477(6):873-883.
14. Bekkenk MW, Jansen PM, Meijer CJ, et al. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. Ann Oncol. 2004;15(7):1097-108.
15. Wu CC, Takahashi E, Asano N, et al. Primary cutaneous NK/T-cell lymphoma of nasal type: an age-related lymphoproliferative disease?. Hum Pathol. 2017;68:61-68.
16. Nicolae A, Ganapathi KA, Pham TH, et al. EBV-negative Aggressive NK-cell Leukemia/Lymphoma: Clinical, Pathologic, and Genetic Features. Am J Surg Pathol. 2017;41(1):67-74.
17. Peck Travis, Wick Mark R. Primary cutaneous natural killer/T-cell lymphoma of the nasal type: a report of 4 cases in North American patients. Ann Diagn Pathol. 2015;19(4): 211-5.
18. Avilés A, Neri N, Fernández R, et al. Combined therapy in untreated patients improves outcome in nasal NK/T lymphoma: results of a clinical trial. Med Oncol. 2013;30(3):637.
19. Kohrt H, Advani R. Extranodal natural killer/T-cell lymphoma: current concepts in biology and treatment. Leuk Lymphoma. 2009;50(11):1773-84.
20. Song GY, Yoon DH, Suh C, et al. Open-label, single arm, multicenter phase II study of VIDL induction chemotherapy followed by upfront autologous stem cell transplantation in patients with advanced stage extranodal NK/T-cell lymphoma. Bone Marrow Transplant. 2021;56(5):1205-1208.
21. Au W Y, Lie A K W, Liang R, et al. Autologous stem cell transplantation for nasal NK/T-cell lymphoma: a progress report on its value. Ann Oncol. 2003;14(11): 1673-6.
22. Choi Y-L, Park J-H, Namkung J-H, et al. Extranodal NK/T-cell lymphoma with cutaneous involvement: 'nasal' vs. 'nasal-type' subgroups–a retrospective study of 18 patients. Br J Dermatol. 2009;160(2): 333-7.
23. Vasconcelos Pedro de, Ferreira Cristina, Soares-Almeida Luís, et al. Multifocal primary cutaneous extranodal NK/T lymphoma nasal type. An Bras Dermatol. 2016;91(2): 219-21.

24. Takata K, Hong ME, Sitthinamsuwan P, et al. Primary cutaneous NK/T-cell lymphoma, nasal type and CD56-positive peripheral T-cell lymphoma: a cellular lineage and clinicopathologic study of 60 patients from Asia. Am J Surg Pathol. 2015;39(1):1-12.
25. Ramesh HS, Boase T, Audisio RA. Risk assessment for cancer surgery in elderly patients. Clin Interv Aging. 2006;1(3):221-7.

Tables

Table. 1 Clinical data of 12 patients with cutaneous extranodal NK/T cell lymphoma

Case No.	Sex	Age (Y)	Diagnosis	Cutaneous involvement	Cutaneous performance	B symptom†	Tretment	Outcome (mo)
1	M	61	PCENKTL	Back,chest,arms	Erythema, ulceration	Fever	C +ASCT	AWD 42
2	M	54	PCENKTL	Left legs	Ulceration	Night sweat	C+R	DOD 24
3	M	35	SCENKTL	Chest	Nodules	None	C	AWD 12
4	M	64	PCENKTL	Nose	Ulceration,crust	Fever	U	DOD 1
5	M	79	SCENKTL	Back,chest	Erythema,nodules	Weight loss	U	DOD 4
6	F	19	PCENKTL	Left legs	Ulceration	Fever	/	/
7	M	73	PCENKTL	Face	Nodules	None	R	DOD 10
8	M	30	SCENKTL	Right legs	Nodules	Night sweat	C+R	DOD 10
9	M	65	PCENKTL	Arms,legs	Ulceration,crust,mass	Fever	C	DOD 3
10	M	92	PCENKTL	Left legs	Ulceration	None	U	AWR 35
11	M	69	SCENKTL	Arms,legs	Ulceration	None	C	DOD 17
12	F	73	PCENKTL	Back,chest	Erythema,mass	Night sweat	U	AWD 1

† B Symptoms: 1. Unexplained fever (> 38℃) for more than 3 consecutive days; 2. Night sweats; 3.Weight loss at 6 months > 10% in months. Abbreviations: PCENKTL, primary cutaneous extranodal natural killer/T-cell lymphoma; SCENKTL, extranodal natural killer/T-cell lymphoma with secondary spread to the skin; C, Chemotherapy; R, Radiotherapy; ASCT, autologous hematopoietic stem cell transplantation ; U, Untreatment; DOD, died of disease; AWD, alive with disease; AWR, alive with recurrence; ”/” means unknown.

Table. 2 Clinical characteristics of cutaneous CENKTL

Characteristics	Total(n = 12)	Percentage
Age,median(range)(years)	64.5(19-92)	
≤60	4	33.3%
60	8	66.7%
Gender		
Male	10	83.3%
Female	2	16.7%
Primary tumor		
Skin	8	66.7%
Nasal Cavity	4	33.3%
Cutaneous involvement		
Solitary	5	41.7%
Multiple	7	58.3%
Distribution of skin lesions		
Head and neck	2	16.7%
Trunk	3	25%
Extremities	6	50%
Generalized	1	8.3%
Clinical features of skin lesions		
Papule or nodules	5	41.7%
Ulceration	7	58.3%
1. Symptoms		
Yes	8	66.7%
No	4	33.3%
LDH level		
Elevated	4	33.3%
Normal	8	66.7%
Ann Arbor Stage		
,	2	16.7%
,	10	83.3%
Treatment		
Chemotherapy	3	25%
Radiotherapy	1	8.3%
Chemotherapy + Radiotherapy	2	16.7%

Chemotherapy + ASCT	1	8.3%
Untreatment	4	33.3%
Unknown	1	8.3%
Outcome		
Survival	4	33.3%
Death	7	58.3%
Unknown	1	8.3%

Figures

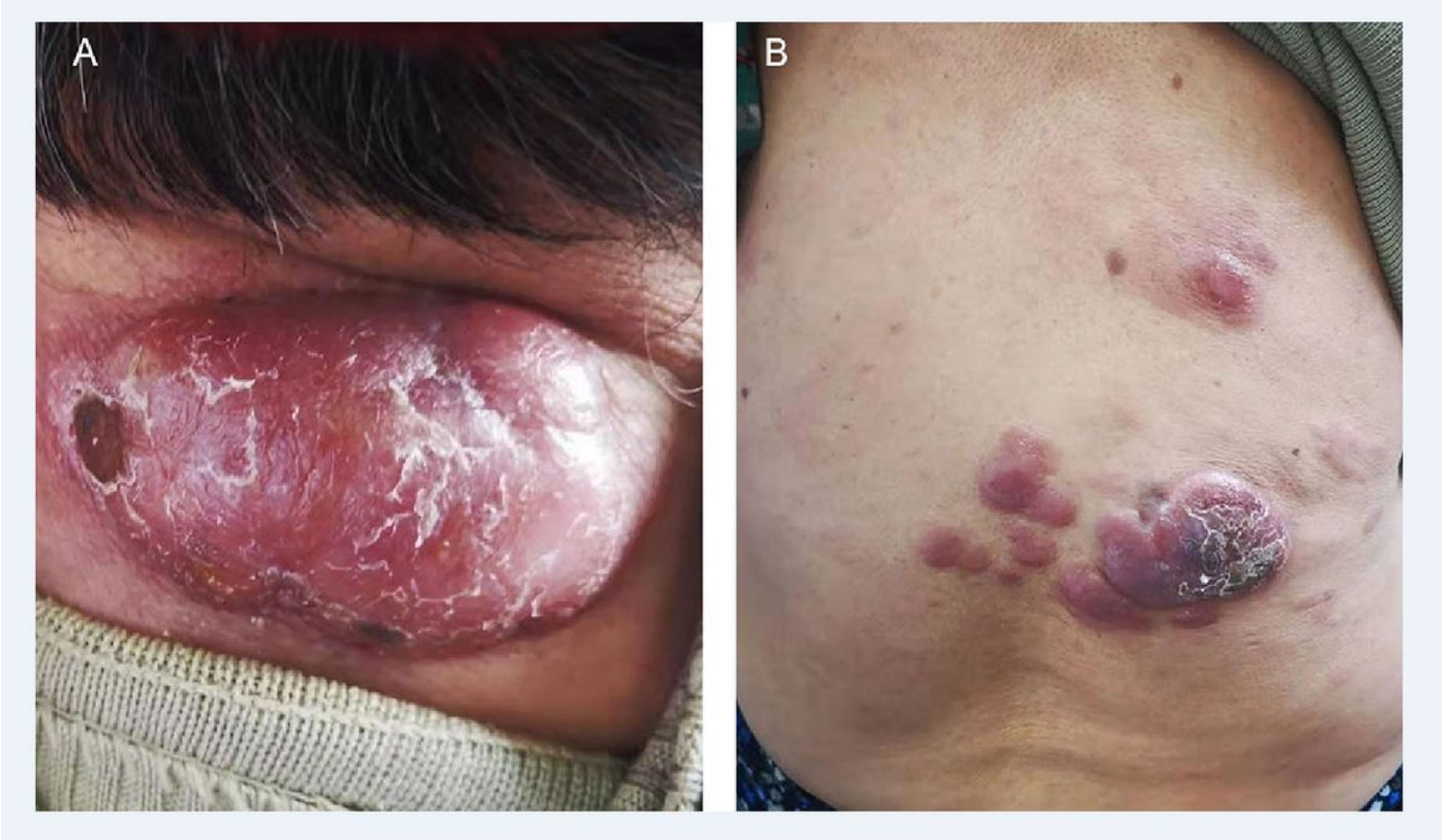

Figure 1

Cutaneous lesions of patients with cutaneous ENKTL A A large mass on the neck. B Multiple erythemas and masses on the back (case 12).

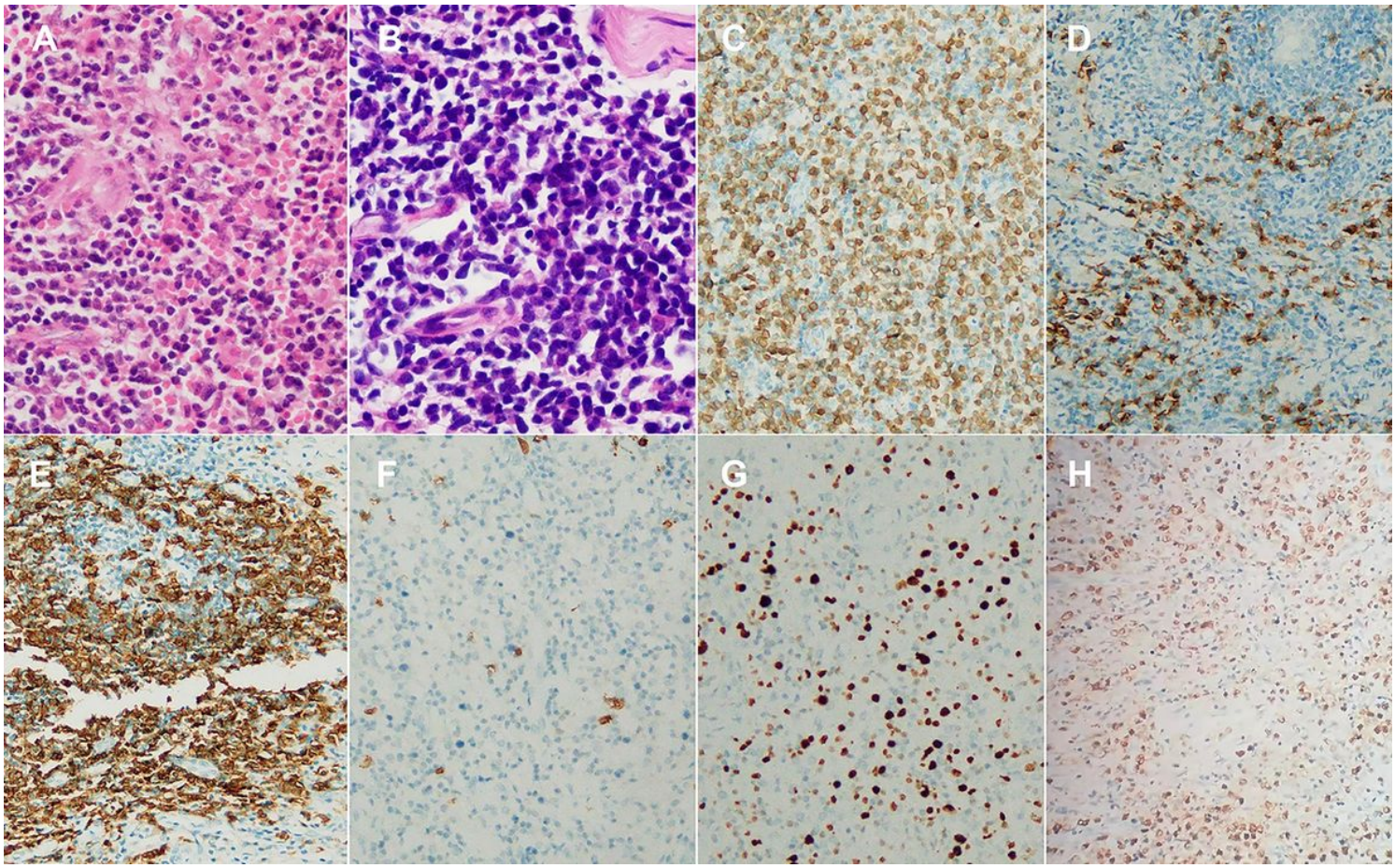

Figure 2

Histomathology and immunohistochemistry of patients with cutaneous ENKTL A-B Histopathology showing a diffuse infiltrating growth of lymphoid cells with dysplasia in the dermis (hematoxylin and eosin stain, ×200). C CD3ε positive (Envision method, ×200). D CD56 positive (Envision method, ×200). E CD20 positive (Envision method, ×200). F CD20 negative (Envision method, ×200). G Ki67 positive(Envision method, ×200). H EBER positive (in situ hybridization, ×200).