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Review Article

Extranodal NK/T-cell lymphoma: diagnosis and treatment cues

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Abstract

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is mostly endemic to East Asia. It predominantly occurs in the nasal or paranasal areas and less frequently in the skin. Most of the tumours show NK-cell, but rarely T-cell, phenotypes. The Epstein–Barr virus (EBV) genome can be usually detected in lymphoma cells. Geographic localization of ENKL matches the endemic distribution of EBV, suggesting that EBV plays an important role in lymphomagenesis. Originally, NK-cell and T-cell types were believed to present the same clinicopathologic characteristics, but recent data suggest more aggressive characteristics for the NK-cell phenotype. Although ENKL is sensitive to radiotherapy, it shows a poorer response to chemotherapeutic agents than other lymphomas due to expression of p-glycoprotein. Therefore, new therapeutic approaches must be considered. Several new clinical trials are now being conducted in East Asia. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: **natural killer cell; azurophilic granule; Epstein–Barr virus; CD56; cytotoxic molecule**

Introduction

Extranodal NK/T-cell lymphoma (ENKL), nasal type most frequently affects the nose and paranasal area [1–3]. The immunophenotype of the lymphoma cells mostly reflects that of NK-cells, but sometimes is also characteristic of T-cells. In some cases differential diagnosis is difficult when only using paraffin embedded specimens. Therefore at present, the diagnostic term 'NK/T-cell lymphoma' is used. It should however be noted that no 'NK/T-cell' actually exists. This type of lymphoma shows a marked geographic preference for East Asia and Latin America. The incidence is also different within the endemic areas; in Asia, the rates of occurrence are: 3.3% in Japan [4], 5% in Taiwan [5], 6% in Hong Kong [6] and 8% in Korea [7]. In this review, we summarize the disease characteristics of ENKL of nasal type with special emphasis on diagnostic pitfalls.

Ontogeny of NK-cells

NK-cells were first defined as a functional subset of lymphocytes that mediate major histocompatibility complex-nonrestricted cytotoxicity [8]. They were later recognized to have large granular lymphocyte (LGL) morphology, germline configurations of T-cell receptor (TCR) and immunoglobulin genes and a surface CD3 (sCD3)-negative and CD56-positive phenotype [9]. From these findings, NK-cells are now regarded as a third lineage of lymphocytes that is distinct from T- and B-cells. Because NK-cells develop from T/NK bi-potential common progenitors (Figure 1) [10,11], they share many similarities with T-cells, particularly with cytotoxic T-cells. Therefore, the phenotypes of NK-cell and T-cell lymphoma/leukaemia also have much in common, which makes it difficult to perform differential diagnosis [12–14].

Pathological transformation of NK-cells

Myeloid antigen-positive T/NK bi-potential progenitors are believed to develop by transformation into myeloid/NK cell precursor acute leukaemia [15,16]. NK-cell lineage committed progenitors are also hypothesized to transform to blastic NK-cell lymphoma (BNKL) or precursor NK-cell acute lymphoblastic leukaemia/lymphoma (NK-ALL) [17,18]. Previously, CD4-positive and CD4-negative types of BNKL/NK-ALL were identified [18]. Although there remain several controversies regarding CD56 expression and dendritic cell lineage, the $CD4^+$ $CD56^+$ type of this tumour is somehow related to plasmacytoid dendritic cells or to the monocytic lineage [19,20], The CD4-negative type probably represents the true BNKL/NK-ALL. Two mature NK-cell neoplasms, ENKL [1] and aggressive NK-cell leukaemia [18d], are transformed from functionally

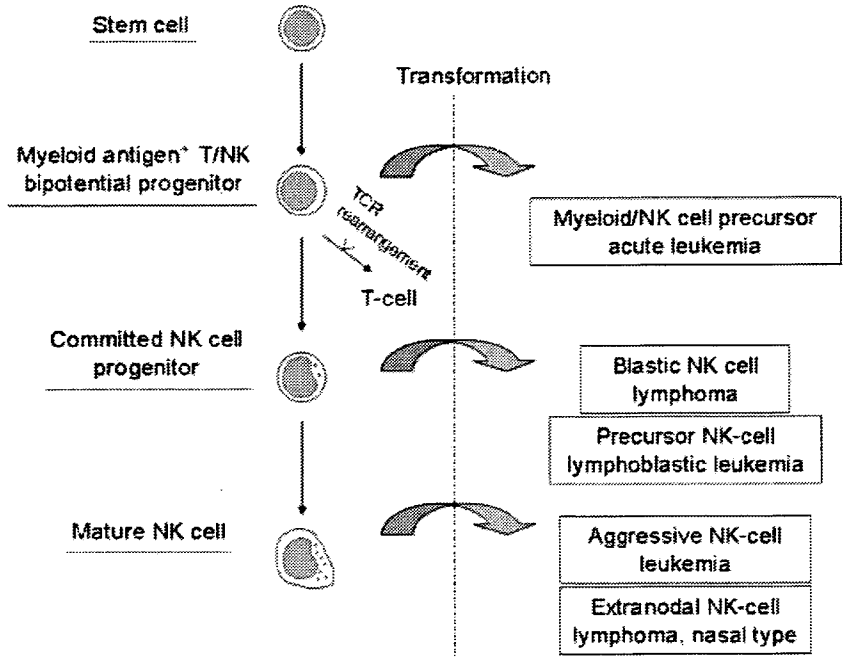

Figure 1. Ontogeny of NK-cells and transformation to NK-cell malignancies. NK-cells are differentiated from stem cells through myeloid-antigen positive NK/T bi-potential progenitors and lineage-committed progenitors. Myeloid/NK cell precursor acute leukaemia is transformed from the myeloid antigen-positive progenitor. Blastic NK-cell lymphoma and precursor NK-cell lymphoblastic leukaemia are derived from a relatively mature, NK-cell lineage committed progenitor. Two mature NK-cell neoplasms, aggressive NK-cell leukaemia and extranodal NK-cell lymphoma, nasal type, are transformed from mature NK-cells

mature NK-cells. Aggressive NK-cell leukaemia is a distinct leukaemic form of mature NK-cell malignancy with frequent hepatosplenic involvement [21,22]. Although these two diseases share many features, several clinicopathologic and phenotypic differences have been reported [23]. Therefore, aggressive NK-cell leukaemia remains as a distinct disease entity in the forthcoming World Health Organization classifications. A summary of the clinicopathologic characteristics of NK-cell lineage neoplasms is given in Table 1.

Clinical characteristics of extranodal NK-cell lymphoma, nasal type

The nose and paranasal area including the upper aerodigestive tract contains the origin of more than 80% of extranodal NK-cell lymphomas, nasal type. Macroscopic findings by nasal endoscope are shown in Figure 2. Initial complaints of ENKL, nasal type include local symptoms such as nasal obstruction, discharge and bleeding. Thereafter, as the disease extends, necrosis, swellingor bony destruction of the nasal area develops. However, such extreme local progressions are currently rare because of early disease recognition and reference to specialized physicians. The skin is the second most frequent organ of origin, accounting for approximately 10% of cases [19]. Cases originating from the liver and/or spleen account for 5% of ENKLs, nasal type. More rare organs of onset include the lung, gastrointestinal tract, kidney, pancreas, testis and brain. Nasal lymphomas more frequently present as a localized disease (ratio 4:1), whereas lymphomas at other sites are more frequently detected at an advanced stage (ratio 2:3) [24–35]. Because this lymphoma essentially presents an extranodal origin, clinical stage III is rare and most of the advanced stage cases are in stage IV. Some cases show long-term limitation to the original site. However, once the tumour develops outside the original site, the disease rapidly progresses and disseminates. Fever, haemophagocytosis and disseminated intravascular coagulation are not rare in this situation. Several cases of stage IV or aggressive NK-cell leukaemia could not be treated because of the progression of the disease and poor status of the patient [36].

Diagnosis of extranodal NK-cell lymphoma, nasal type

Diagnosis of ENKL, nasal-type is based on histopathologic examination of biopsy specimens, but is sometimes difficult because of the existence of wide necrosis around the tumour (Figure 3A) that is characterized by expression of Fas and Fas ligand on the tumour cells [37]. Selection of appropriate sites for biopsy is important for prompt diagnosis, as are repeated approaches in case the specimens only include necrotic tissue.

Histologically, tumour cells from ENKL generally show angiocentric growth pattern (Figure 3A) [1,38]. The growth pattern is such a notable feature of this lymphoma that the diagnostic term used to be 'angiocentric lymphoma' [39]. In clinical practice, sampling error can prevent recognition of angiocentricity; therefore this finding is currently not mandatory for diagnosis [38]. The presence of cucumber-

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Table 1. Clinicopathologic characteristics of NK-cell lineage neoplasms

	Myeloid/NK cell precursor acute leukaemia	Blastic NK-cell lymphoma/Precursor NK-cell lymphoblastic leukaemia	Aggressive NK-cell leukaemia	Extranodal NK cell lymphoma, nasal type	
				Limited stage	Advanced stage
Morphology	Blastic	Blastic	LGL	LGL	
Azurophilic granule	−	−	+	+	
Lymph node involvement	+	+	+	−	+/−
Extranodal involvement	Bone marrow, blood, mediastinum	Skin, bone marrow	Bone marrow, blood, liver, spleen	Nose, skin	Nose, skin, bone marrow, blood
B-symptom	Rare	Rare	Frequent	Rare	Frequent
Surface marker	CD7+, CD33+, CD34+, CD56+	CD4+/−, CD7+, CD56+, TdT+	CD2+, CD16+, CD56+	CD2+, cyCD3+, CD56+	
EBV	−	−	+/−	+	
Clinical course	Aggressive	Aggressive	Aggressive	Sometimes indolent	Aggressive
Therapy	AML chemotherapy	Chemotherapy for lymphoid neoplasms	No standard therapy	Radiotherapy followed by chemotherapy	No standard therapy
Prognosis	Relapse is frequent, and the prognosis is poor.	Relapse is frequent, and the prognosis is poor.	Very poor	Fair	Very poor

LGL, large granular lymphocyte; EBV, Epstein–Barr virus; AML, acute myeloid leukaemia.

Figure 2. Naso-endoscopic findings of nasal NK/T-cell lymphoma. (A) Naso-endoscopic findings of a patient who presented with nasal discharge. Tumour formation and tissue swelling by necrosis can be observed. (B) Surface ulcerations can be seen, and a part of the nasal cartilage was destroyed

like cells with elongated nuclei is particular to ENKL, and is helpful for diagnosis (Figure 3B). If the biopsy specimen is small, a touch imprint smear with Giemsa staining is sometimes useful for diagnosis because of the presence of azurophilic granules in the tumour cells (Figure 4). The accumulation of NK-cells or cytotoxic T-cells does not directly indicate a malignant condition; however, since it is not usually recognized in the nasal mucosa, the assemblage of NK-cells (or rarely cytotoxic T-cells) is still important evidence. Epstein–Barr virus (EBV) is harboured in ENKLs of nasal type, and detection by *in situ* hybridization can be achieved for paraffin-embedded tissues or touch imprint smears (Figure 5). EBV is rarely observed in

Figure 3. Biopsy specimen of nasal NK/T-cell lymphoma. (A) In a vast necrotic region, there exist several atypical medium-to-large lymphocytes. Tumour cells show an angiocentric growth pattern. (B) The nuclei of several tumour cells are elongated, and present a cucumber-like morphology (Arrow)

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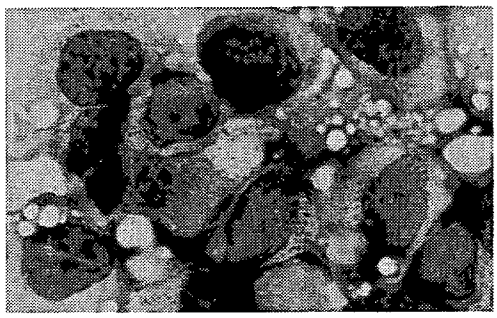

Figure 4. Touch imprint smear of ENKL. There are many atypical NK-cells with prominent azurophilic granules

lymphocytes residing in normal or inflammatory nasal mucosa or adjacent tissue; therefore detection is particularly important for specimens that mostly consist of necrotic tissue.

For ENKLs, histopathologic diagnosis of bone marrow involvement is occasionally difficult. Detection of EBV is also helpful in this situation [40]. Recently, the prognostic significance of such occult or minute involvement has been shown for early stage patients [41]. Routine examination of bone marrow involvement by using EBV *in situ* hybridization is now recommended.

Immunophenotype of extranodal NK-cell lymphoma, nasal type

Phenotypic markers expressed in ENKL include CD2, cytoplasmic CD3 (cyCD3), CD7 and CD56, which also represent the phenotype of normal NK-cells [25,42,43]. Cytotoxic molecules such as TIA-1, granzyme B and perforin, are also positive in ENKL [37,44]. Table 1 shows the differential diagnosis of mature NK-cell tumours. If lymphoma cells are negative for these cytotoxic molecules and show a T-cell phenotype, diagnosis of another type of T-cell lymphoma should be considered. For differentiation of NK-cell from T-cell lymphoma, expression of sCD3, CD5 or TCRs on the lymphoma cells can be evaluated [31,43,45], in addition to the rearrangement of TCR genes. However, routine diagnostic use of these procedures is sometimes difficult and unavailable. Previously, the clinical features and prognosis of true T-cell nasal lymphoma were regarded to be similar to that of NK-cell type, resulting in the adoption of the term 'NK/T-cell lymphoma'. It should be noted, however, that this nomenclature falsely suggests existence of 'NK/T-cells'. Another point to be noted is that the use of the term 'NK/T' is restricted to lymphomas occurring in the nasal/paranasal area, and is not applied to lymphomas originated from extra-nasal sites. Differential diagnosis from other types of T-cell lymphomas is therefore required for the extra-nasal type of extranodal NK-cell lymphoma.

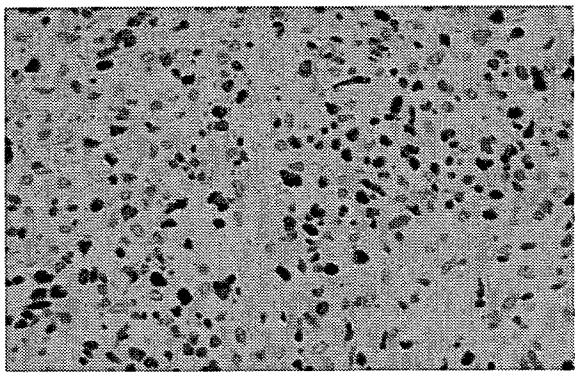

Figure 5. Epstein–Barr virus small RNA (EBER) in-situ hybridization (ISH). Because lymphoma cells harbour the EBV, they are positive for EBER-ISH

Recently, studies with large numbers of patients showed that the prognosis of nasal NK-cell lymphoma is significantly poorer than that of nasal 'T-cell' lymphoma [29,46]. Differential diagnosis of NK-cell lymphoma from genuine T-cell lymphoma may therefore be required in the future. A search for a diagnostic marker is therefore warranted.

Diagnostic pitfalls for extranodal NK/T-cell lymphoma

Because CD56 is also expressed in a part of acute myeloid leukaemia (AML) [47], differential diagnosis of NK-cell malignancies from CD56-positive AML is occasionally difficult, particularly for those with extramedullary or cutaneous involvement. $CD4^+$ $CD56^+$ haematodermic neoplasm also frequently shows cutaneous/subcutaneous involvement [18,19]. In this context, CD56-positive AML and $CD4^+$ $CD56^+$ haematodermic neoplasm are unexceptionally negative for EBV, which is useful for the differential diagnosis. Positive EBV status is thus required for the diagnosis of NK/T-cell lymphomas.

Treatment of extranodal NK/T-cell lymphoma

Limited stages

For limited stages of usual aggressive non-Hodgkin lymphoma, three to four courses of a chemotherapy regimen that includes anthracycline, such as CHOP, supplemented with involved field irradiation is regarded as the standard therapy [48]. However, for nasal NK/T-cell lymphoma, the overall 5-year survival rate using this strategy is less than 50% [49,50]. Reasons include the expression of the multidrug-resistant p-glycoprotein in NK/T-cell lymphoma cells [51,52]. P-glycoprotein actively exports doxorubicin and vincristine, which are the main components of CHOP chemotherapy. Radiotherapy remains effective but cannot prevent recurrence of the disease outside the radiation field. The overall 5-year survival rate therefore remains limited to 40–50% when using radiotherapy alone [31,53,54].

Ribrag *et al.* treated eight patients in the limited stage of nasal NK/T-cell lymphoma with radiotherapy followed by chemotherapy and reported an excellent result (10 years overall survival: 100%) [55]. They have concluded that a sufficient dose of radiotherapy immediately after diagnosis

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is desirable for treatment of this disease. At present, radiotherapy followed by chemotherapy is regarded as a standard strategy for limited stage ENKL [31,56].

Yamaguchi *et al.* also reported excellent control of the disease by simultaneous chemoradiotherapy using radiation therapy and DeVIC chemotherapy (RT-DeVIC) [50]. Based on this finding, the Japanese Clinical Oncology Group has conducted a phase I/II study of RT-DeVIC chemoradiotherapy. The study is now closed with sufficient numbers of patients registered. Its results are anticipated.

Advanced stages

The prognosis of advanced stage ENKL, nasal type, as well as that of aggressive NK-cell leukaemia, is extremely poor when using any chemotherapeutic regimen [22]. Aviles *et al.* from Mexico reported the utility of sandwich chemoradiotherapy, which consisted of three courses of cyclophosphamide, methotrexate, etoposide and dexamethasone (CMED), radiotherapy and additional three courses of CMED. The 5-year overall survival rate using this method was reported as 65% [57]. This was an excellent result, but the reported toxicities were surprisingly low despite the relatively high dose of chemotherapeutic drugs used. Therefore, confirmation through replication is required.

Recently, several reports from East Asia suggest the efficacy of L-asparaginase for treatment of mature NK/T-cell lymphoma [58–60]. L-asparaginase is an enzyme that digests serum L-asparagine and acts as an anti-tumour agent through asparagine starvation of tumours with low expression levels of asparagine synthetase [61,62]. Because L-asparaginase specifically acts on lymphoid cells, myelosuppression by L-asparaginase is minimal. L-asparaginase has long been regarded as a key drug for paediatric acute lymphoblastic leukaemia. A Chinese group treated nasal NK/T-cell lymphoma patients refractory to CHOP-like chemotherapy with a chemotherapy regimen that consisted of L-asparaginase, vincristine and dexamethasone supplemented by local radiotherapy. They reported good results with a 5-year overall survival rate of 55.6% [63]. Likewise, L-asparaginase is effective for this type of lymphoma but has many adverse reactions such as haemostatic complications, allergy and pancreatitis. These findings suggest a need for the establishment of safe and effective chemotherapeutic regimens. The NK-cell Tumour Study Group is now conducting clinical studies of a novel L-asparaginase-containing chemotherapy for initial stage IV, relapsed or refractory NK/T-cell leukaemia/lymphoma [36]. This regimen is termed SMILE, and consists of methotrexate, ifosfamide, etoposide, steroid and L-asparaginase. A phase I dose finding study has been completed [64] and we are now designing a subsequent phase II study.

Haematopoietic stem cell transplantation (HSCT)

Because the prognosis of ENKL is poor, there exist several reports of upfront autologous HSCT. In large-scale reports from Japan and Korea, long-term survival ranges from 50 to 70% [65–67]. However, retrospective analysis might be biased by patient selection. Prospective clinical trials are thus warranted before concluding that autologous HSCT is effective for ENKL.

On the other hand, allogeneic HSCT can also be applied for the treatment and is the only curative strategy for advanced stage or nonremission patients. Two large-scale analyses from Japan included high-risk patients and reported a long-term survival rate ranging from 30 to 40% [66,68]. The second study included patients who received reduced intensity stem cell transplants (RIST), and both reports indicated the absence of late recurrence at 2 years post-transplantation. These findings suggest the curative potential of allogeneic HSCT, but patient selection bias is also possible. Since many types of stem cell sources are now utilized for HSCT including cord blood and mismatched donors, further accumulation of data and prospective evaluations are also required.

Clinical significance of the Epstein–Barr virus

It is well-known that patient sera from EBV-positive malignancies contain fragmented viral DNA [69,70]. Measurement of the circulating viral DNA load in peripheral blood is useful for diagnosis, monitoring and prognostication of the disease. However, detection is sometimes misunderstood as the presence of viral particle itself; rather, the detected DNA is derived from dead tumour cells. For these reasons, most detected fragments are less than 500 bp in length, and longer fragments or the entire EBV genome are never detected [71]. EBV-DNA can therefore be used as a marker to predict the tumour burden [72,73], but prediction can potentially be affected by the presence of EBV unrelated to the lymphoma. There are several choices of source tissue for analysis including plasma, total blood and mononuclear cells, and each choice represents a different outcome [74]. The significance of the viral load in peripheral blood and the choice of source tissue used for analysis should be examined prospectively.

Conclusion

Several new insights have been recently developed for extranasal NK/T-cell lymphoma, nasal type. Diagnosis is thus becoming easier. However, the prognosis is particularly poor in both the limited and advanced stages. Appropriate therapeutic strategies should be explored by prospective studies.

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