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Extranodal NK/T-cell lymphoma: Updates in biology and management strategies

Motoko Yamaguchi[a,*], Masahiko Oguchi[b], Ritsuro Suzuki[c]

[a] Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, Japan
[b] Department of Radiation Oncology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan
[c] Department of Oncology/Hematology, Shimane University Hospital, Izumo, Japan

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ABSTRACT

Extranodal NK/T-cell lymphoma, nasal type (ENKL), is a rare lymphoma subtype of peripheral T/NK-cell lymphoma that is very common in East Asia and Latin America. Two-thirds of patients have localized disease in the nasal cavity or adjacent sites. Large retrospective studies have revealed the clinicopathologic features of ENKL patients, identified risk factors for short survival time, and developed prognostic models. Next-generation sequencing studies have provided a comprehensive list of recurrent mutations in ENKL. Since the early 2000s, disease-specific therapeutic approaches have been developed, and the standard of care for ENKL has markedly changed. Non-anthracycline-containing chemotherapy with or without radiotherapy is the current standard approach for ENKL treatment. Emerging therapies, including the use of immune checkpoint inhibitors, are being investigated.

1. Introduction

Extranodal natural killer/T-cell lymphoma, nasal type (ENKL), is a rare lymphoid neoplasm characterized by an association with Epstein-Barr virus (EBV) [1]. The most frequent occurrence sites include the nasal cavity and adjacent sites. Many reviews have discussed the genetic and clinicopathologic features of ENKL, its association with EBV, and therapeutic advances [2–8]. In this review, we will update the current knowledge of the molecular features of ENKL and discuss the results of recent clinical studies that are relevant to the current and future management of this disease.

2. Expression of surface and intracellular molecules in ENKL tumour cells

ENKL tumour cells commonly express cytoplasmic CD3, CD56, and cytotoxic proteins including perforin, granzyme B, and TIA1 and are usually negative for surface CD3, CD4, and CD5 expression. The expression of these molecules and EBV-encoded RNA (EBER) *in situ* hybridization are used for diagnosis in clinical practice.

P-glycoprotein is frequently expressed in ENKL cells [9–11]. An international study identified Ki-67 positivity > 50% as a survival risk factor for patients with ENKL [12]. Retrospective immunohistochemical analyses revealed the prognostic significance of the expression of granzyme B protease inhibitor 9 (PI9) [13] or cyclooxygenase-2 (COX-2) [14] in ENKL.

Among the surface molecules that are targeted by available agents, CD38 is expressed in the majority of patients with ENKL [15].

* Corresponding author. Department of Hematology and Oncology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan.
E-mail address: myamaguchi@clin.medic.mie-u.ac.jp (M. Yamaguchi).

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Table 1
Reported frequencies of gene mutations in ENKL.

Reference	[38]	[39]	[40]	[41]
	n = 25	n = 34	n = 105	n = 25
JAK3	0%	6%	0%	8%
STAT3	12%	27%	11%	8%
STAT5B	4%	0%	2%	0%
DDX3X	4%	0%	20%	12%
BCOR	16%	21%	0%	32%
TP53	8%	12%	13%	16%

A good response to CD38 antibody (daratumumab) monotherapy was documented in a patient with refractory ENKL [16]. A phase I study of the single agent daratumumab for relapsed or refractory ENKL is ongoing in East Asia. CD30 is positive in > 50% of patients with ENKL [17]. Several prospective clinical trials of the single agent brentuximab vedotin for ENKL are being conducted [18]. CD52 is expressed in a quarter of patients with ENKL [19], but there are few reports describing the use of alemtuzumab, a humanized CD52 antibody, in the treatment of ENKL [20,21]. CC chemokine receptor 4 (CCR4) is rarely expressed in ENKL (1/27, 3.7%) [22], and to the best of our knowledge, there is no report of the use of mogamulizumab, an antibody drug targeting CCR4, for the treatment of ENKL. Programmed cell death ligand 1 (PD-L1) is expressed in the tumour cells of > 80% of patients with ENKL [23–26], and there are some reports describing the use of PD-1 antibodies in patients with relapsed or refractory ENKL (see below).

3. Molecular aberration in ENKL

Early conventional chromosomal analyses identified del(6)(q21q25) as a recurrent chromosomal abnormality in ENKL [27]. Subsequently, comparative genomic hybridization studies confirmed that the deletion of chromosome 6q is frequently observed in ENKL [28–30]. Based on analyses of 6q, including gene expression profiling (GEP), *PRDM1*, *FOXO3*, and *PTPRK*, were identified as putative tumour suppressor genes [31–33]. GEP studies also revealed that the molecular signatures of ENKL are distinct from those of the αβ-T-cell type peripheral T-cell lymphoma (PTCL) and hepatosplenic T-cell lymphoma [34]. By contrast, the molecular signatures of the γδ-T-cell type of ENKL and NK-cell type ENKL are very similar [35]. A high expression of genes of cytotoxic molecules, particularly granzyme H, and deregulation of the AKT, NF-κB, and JAK-STAT3 pathways, was detected in ENKL [31].

Early studies demonstrated mutations of tumour suppressor genes in ENKL. *FAS* mutations are detected in 50% of patients with ENKL [36], and *TP53* is mutated in < 50% of patients [37]. Since 2012, the advent of next-generation sequencing has uncovered the genomic landscape in ENKL. Table 1 summarizes the frequencies of recurrent gene mutations in ENKL that were reported in studies including > 20 cases [38–41]. Recurrent gene mutations in the JAK-STAT pathway have been reported. Although the frequency of *JAK3* mutations in ENKL is low (0–8%) [38–43], ENKL cells are frequently positive for phosphorylated *JAK3* [42,44]. In contrast, the frequencies of *STAT3* mutations in previous reports is relatively high (8–27%, Table 1), and most ENKL cases are positive for pSTAT3 expression [45]. These data indicate that *STAT3* may be more promising than *JAK3* as a therapeutic target in ENKL. The RNA helicase gene *DDX3X* is mutated in 0–20% of patients [38–41]. *DDX3X* mutations were more frequently detected in male patients than in female patients and were associated with short overall survival [40]. The BCL6 interacting co-repressor *BCOR* is mutated in 0–32% of patients with ENKL [38–41]. Among the lymphoid malignancies, *BCOR* mutations are restricted to ENKL.

Hemophagocytic syndrome (HPS) sometimes occurs in patients with ENKL. In a study including whole exome sequencing, a hotspot mutation (T419C) was found encoding a V140A variant of an *evolutionarily conserved signalling intermediate in Toll pathway (ECSIT)* [46]. *ECSIT*-V140A was associated with a high incidence of HPS, the activation of NK-κB, and a poor prognosis in an analysis of 81 patients with ENKL. The mean age of patients with an *ECSIT* mutation in the study was 31.4 years, and most had extranasal ENKL, suggesting that *ECSIT* mutations identify a particular cohort of patients who are at risk for HPS.

4. Management strategies for ENKL

4.1. Prognostic models

Currently, the prognostic index of natural killer lymphoma (PINK) is used as a prognostic model for patients with ENKL [47]. In 2016, PINK was proposed as a model for patients who received non-anthracycline-containing chemotherapy with or without radiotherapy or radiotherapy with curative intent, which are current therapeutic approaches. Independent risk factors of PINK include age > 60 years, stage III or IV disease, distant lymph node involvement, and non-nasal type disease. The PINK model is particularly useful in discriminating patients who should be treated for advanced disease. For example, patients with localized nasal ENKL with distant lymph node involvement (axillary, infraclavicular, or mediastinal lymph nodes) should be treated with intensive therapy for advanced ENKL. A prognostic model, including circulating EBV-DNA, was also proposed (PINK-E) [47]. The NK/T-cell lymphoma prognostic index (NK-PI) [48], which was proposed in 2006 and was widely used in ENKL, is not prognostic in the era of non-anthracycline-containing therapies [49]. The International Prognostic Index remains valid in ENKL [50], but the value is limited because most patients with localized ENKL are classified into low or low-intermediate risk categories.