Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal-type, is a distinct clinicopathologic entity according to the Revised European American Lymphoma (REAL)/World Health Organization (WHO) classification of lymphoid tissue [5, 9]. Clinically, this entity is characterized by a predominance in males, young age of onset, a large proportion of early stage diseases, frequent systematic symptoms, good performance, low-risk international prognostic index (IPI), and a propensity for extranodal spread [7, 30, 31, 50]. Extranodal nasal-type NK/T-cell lymphoma (NK/TCL) is highly sensitive to radiotherapy but refractory to doxorubicin-based chemotherapy.

The management of extranodal nasal-type NK/TCL has been based largely on extrapolation from the experience with aggressive non-Hodgkin’s lymphoma (NHL) or diffuse large B-cell lymphoma. The prognosis and optimal therapy of this particular disease have been largely undetermined, due to the small series, heterogeneous treatments, and variable diagnostic criteria. Reported overall survival displays wide variations between the series [2, 4, 6, 7, 10-12, 15-21, 30-31, 38, 50]. The aim of this chapter is to review the clinical features and advances in treatment for this relatively uncommon disease.
**Incidence**

Extranodal NK/TCL, nasal-type, shows variations in incidence in different populations and geographic locations. It is a rare disease in the United States and Europe [4, 37], but it is relatively common in Asian and Latin American countries such as China, Korea and Mexico [2, 23-27, 29-32]. Extranodal nasal-type NK/TCL accounts for 2-10% of all NHL cases in China [6, 10, 27-32, 38].

**Pathology**

Extranodal nasal-type NK/TCL represents a heterogeneous group of lymphomas based on the major site of involvement, of which the nasal cavity is the most common site [20, 24-26, 30]. The term “nasal NK/T-cell lymphoma” is used only for those cases presenting in the nasal cavity with or without involvement of adjacent organs or tissues. The histological features of extranodal nasal-type NK/TCL are similar irrespective of the anatomical sites involved [22]. Tumours with an identical morphology and phenotype occur in the extra-nasal sites, mostly in the Waldeyer ring, skin, gastrointestinal tract and soft tissue, are referred to as nasal-type NK/T-cell lymphoma. Extranodal nasal-type NK/TCL was formerly called angiocentric T-cell lymphoma in the REAL classification in 1994, and many other terms including lethal midline granuloma, malignant granuloma, midline malignant reticulosis, and angiocentric immunoproliferative lesion have been clinically used before 1994 [5, 9].

The morphology of this disease shows several typical features including angiocentricity, angioinvasion, zone-necrosis, and polymorphism of individual cells. It is characterized by a broad cytologic spectrum with small or medium size of tumour cells and polymorphous inflammatory infiltrate. Repeated biopsy is usually required for pathologic diagnosis, due to extensive necrosis and the small size of specimens.

The typical phenotype is CD2+, surface CD3-, cytoplasmic CD3+, CD56+, CD20-/CD79a-, cytotoxic molecules (T-cell Intracellular Antigen-1 [TIA-1], GRanzyme B, Perforin)+, and Epstein-Barr virus (EBV) +. CD43, CD45RO, Fas (CD95) and Fas ligand are commonly expressed [5, 9]. Other NK-cell and T-cell markers are usually negative: CD4, CD8, CD16, CD57, and T-cell receptor (TCR). The criteria of immunopathological diagnosis include CD2+CD56+, surface CD3- and cytoplasmic CD3+ (NK-cell origin). Additionally, many studies include cytotoxic T-cell lymphomas expressing CD3e+, CD56-, cytotoxic molecule (TIA, Gram B, Perforin)+, and EBV+. However, nasal or other extranodal lymphomas that are CDe+CD56-, but negative for cytotoxic molecules and EBV should be diagnosed as peripheral T-cell lymphoma. Extranodal nasal-type NK/TCL is postulated to originate from immature (activated) NK-cells or rarely, from a subset of cytotoxic T-cell lymphocytes. There is no difference in survival or clinicopathologic features between the true NK-cell lymphomas and their T-cell counterparts.

TCR and immunoglobulin gene rearrangements are usually absent. EBV genomes are usually present, and are detectable in the majority of patients by in-situ hybridization for EBER-1. EBV infection is observed in more than 90% of nasal NK/T-cell lymphoma cases [12, 22]. In contrast, EBV expression is relatively low (40-76%) for patients with extranasal NK/TCL [8, 22]. Loss of heterozygosity within chromosome 6q, overexpression of matrix metalloproteinase 9, and interleukin-9 have been observed in this disease [4, 35, 43]. The inactivation or mutation of p53 is a common occurrence in NK/TCL [39].