NK-Cell Lymphomas and Leukemias

A Spectrum of Tumors With Variable Manifestations and Immunophenotype

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Abstract

Natural killer (NK) cells are lymphocytes that have some phenotypic and functional similarities to cytotoxic T cells but do not express the T-cell receptor complex. NK-cell malignancies may be localized or disseminated at initial examination, and most behave aggressively. The variable presentation of NK-cell lymphomas and leukemias suggests that they represent a spectrum of disease, with Epstein-Barr virus (EBV) implicated in the pathogenesis of most cases. Using cases presented in Session 10 of the 2005 Society for Hematopathology/European Association for Haematopathology Workshop on T-cell and NK-cell malignancies, we discuss outstanding issues in the classification and diagnosis of NK-cell malignancies. These difficulties are related to unusual sites of manifestation, atypical immunophenotypic features, and EBV+ T-cell tumors that resemble classical extranodal NK/T-cell lymphoma, nasal-type (EN-NK/T-NT). Although some of these cases can be grouped into EN-NK/T-NT, classification of tumors that have atypical or discordant features will remain controversial, particularly when EBV is absent.

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (EN-NK/T-NT) is most common in Asia and Central and South America and affects adults, with a male predominance.[1-3] It classically arises in the nasal cavity or surrounding structures, such as the sinuses or palate. Morphologically, this tumor exhibits an angiocentric and angiodestructive growth pattern, with associated geographic necrosis and ulceration. The tumor cell cytologic picture varies from small to large and anaplastic, and the tumor cells are often accompanied by numerous nonneoplastic inflammatory cells, such as plasma cells, histiocytes, and eosinophils.

The typical immunophenotype of EN-NK/T-NT shares some features with normal NK cells (CD2+, CD56+, and surface CD3–), although unlike normal NK cells, these tumors are usually CD7– and CD16–. The tumor cells express the ε chain of CD3 in their cytoplasm and, therefore, often stain positively for CD3 by immunohistochemical staining of paraffin sections.[4] Cases express the cytotoxic granule–associated proteins granzyme B, T-cell–restricted intracellular antigen (TIA-1), and perforin. Like normal NK cells, EN-NK/T-NT typically does not exhibit rearrangement of T-cell receptor (TCR) or immunoglobulin genes. Epstein-Barr virus (EBV) is present in the neoplastic cells in clonal episomal form, strongly implying a role for this virus in tumor pathogenesis.[5-7]

As implied by the designation nasal-type, this tumor may also occur in other sites in the upper aerodigestive tract and in other extranodal sites such as the skin, gastrointestinal tract, testis, and soft tissue,[1] as discussed subsequently. The disease may be predominantly localized or may be disseminated at initial examination, involving liver, spleen, skin, and/or bone marrow.[3,7,8] Although the disease is clinically aggressive, many patients enjoy long-term survival after treatment with combined chemoradiotherapy.[9,10]

Aggressive NK-cell leukemia is a rare, clinically aggressive leukemic form of NK-cell neoplasia. It shares many features with EN-NK/T-NT, such as prevalence among Asians, strong association with EBV, and a similar immunophenotype. Because EN-NK/T-NT also may involve bone marrow and both diseases are often associated with a hemophagocytic syndrome, some authors believe that aggressive NK-cell leukemia represents a leukemic form of EN-NK/T-NT, akin to the relationship between lymphoblastic lymphoma and leukemia.[1,2,11]

Although the features of classical NK/T-cell lymphoma and leukemia are well-accepted **Table 1**, cases that differ in 1 or more features occur and may cause problems in differential diagnosis with other neoplasms, in particular cytotoxic extranodal peripheral T-cell lymphomas (PTCLs). The Workshop included typical cases of EN-NK/T-NT and cases that challenged the borders of the classic definition. These cases raised several questions pertaining to the appropriate classification of lymphomas exhibiting NK features.

Location, Location, Location: Which Extranodal Sites of Involvement Are Compatible With a Diagnosis of EN-NK/T-NT?

EN-NK/T-NT classically arises in the nasal cavity or in nearby sites such as the palate or sinuses. A classic example of nasal-type NK/T-cell lymphoma from the Workshop shows angioinvasion and extensive apoptosis and necrosis **Image 1**. The differential diagnosis of this type of lymphoma often includes a reactive, inflammatory process. Histologic clues to the diagnosis of lymphoma include invasion of underlying bone and extensive ulceration. Demonstration of aberrant loss of NK/T-cell antigens, CD56 expression, and EBV small-encoded RNA (EBER) positivity are helpful in establishing the diagnosis of lymphoma.

EN-NK/T-NT can disseminate to other extranodal sites such as skin, gastrointestinal tract, testis, skin, and even pancreas, and it is also generally accepted that this tumor can arise in these sites without involving the classic nasal location.[1,2,12,13] EN-NK/T-NT arising in the skin, with no evidence of sinonasal involvement, usually has a differential diagnosis of pleomorphic/transformed mycosis fungoides, PTCL unspecified, or the CD4+/CD56+ hematodermic malignancy. Cases arising in the small intestine with or without involvement of the adjacent lymph nodes have a differential diagnosis with enteropathy-type T-cell lymphoma. Other more unusual extranodal sites of EN-NK/T-NT seen at the Workshop included the adrenal gland and female genital tract (uterus and ovaries). It was the consensus of the Workshop expert panel and the participants that these extranodal locations could be accepted in the spectrum of presenting sites for EN-NK/T-NT because their features were otherwise acceptable for the diagnosis.

If features are otherwise typical, the diagnosis of EN-NK/T-NT can be established in a wide variety of extranodal sites.

Table 1
"Classic" Features of Extranodal NK/T-Cell Lymphoma, Nasal Type and Aggressive NK-Cell Leukemia

	Feature
Epidemiology	Asian and Central and South American adults
Location	Anterior nasal cavity or leukemic
Morphologic features	Angiodestructive with admixed inflammatory infiltrate and necrosis (lymphoma)
Immunophenotype	CD2+, CD56+, cytoplasmic CD3ε+, surface CD3–, CD5–, CD4–, CD8–
EBV status	EBER+, clonal episomal EBV in tumor cells
T-cell receptor genes	Germline

EBER, EBV small-encoded RNA; EBV, Epstein-Barr virus; NK, natural killer.

Can EN-NK/T-NT Manifest as a Primary Nodal Disease, Without Evidence of Extranodal Involvement?

Two Workshop cases were submitted as nodal manifestations of EN-NK/T-NT. In a case of unilateral cervical lymphadenopathy, without involvement of the nasopharynx, the neoplasm displayed an unusual sinusoidal pattern of lymph node infiltration and did not show the angiodestruction characteristic of EN-NK/T-NT **Image 2**. However, the immunophenotype and positivity for EBER were typical, favoring its classification as an EN-NK/T-NT rather than as a PTCL unspecified.

Another case manifested in a cervical lymph node and displayed a "folliculotropic" pattern of nodal infiltration **Image 3**. There was also focal involvement of the trachea, but the bulk of disease was nodal. This case was EBER–, although it expressed CD56 and cytotoxic granule–associated proteins and lacked clonal TCR gene rearrangements. The differential classification between EN-NK/T-NT and PTCL unspecified was raised.

EN-NK/T-NT can rarely manifest as a primary nodal disease, but immunophenotypic features should be typical and EBV should be demonstrated. There was no consensus on how to classify nodal lymphomas with an apparent NK-cell phenotype and genotype that are negative for EBV.

What Is the Morphologic Spectrum of EN-NK/T-NT?

The morphologic spectrum of EN-NK/T-NT includes cases with a low-grade appearance mimicking reactive infiltrates as shown in 1 Workshop case **Image 4A** and **Image 4B**. This case remained indolent for 10 years before

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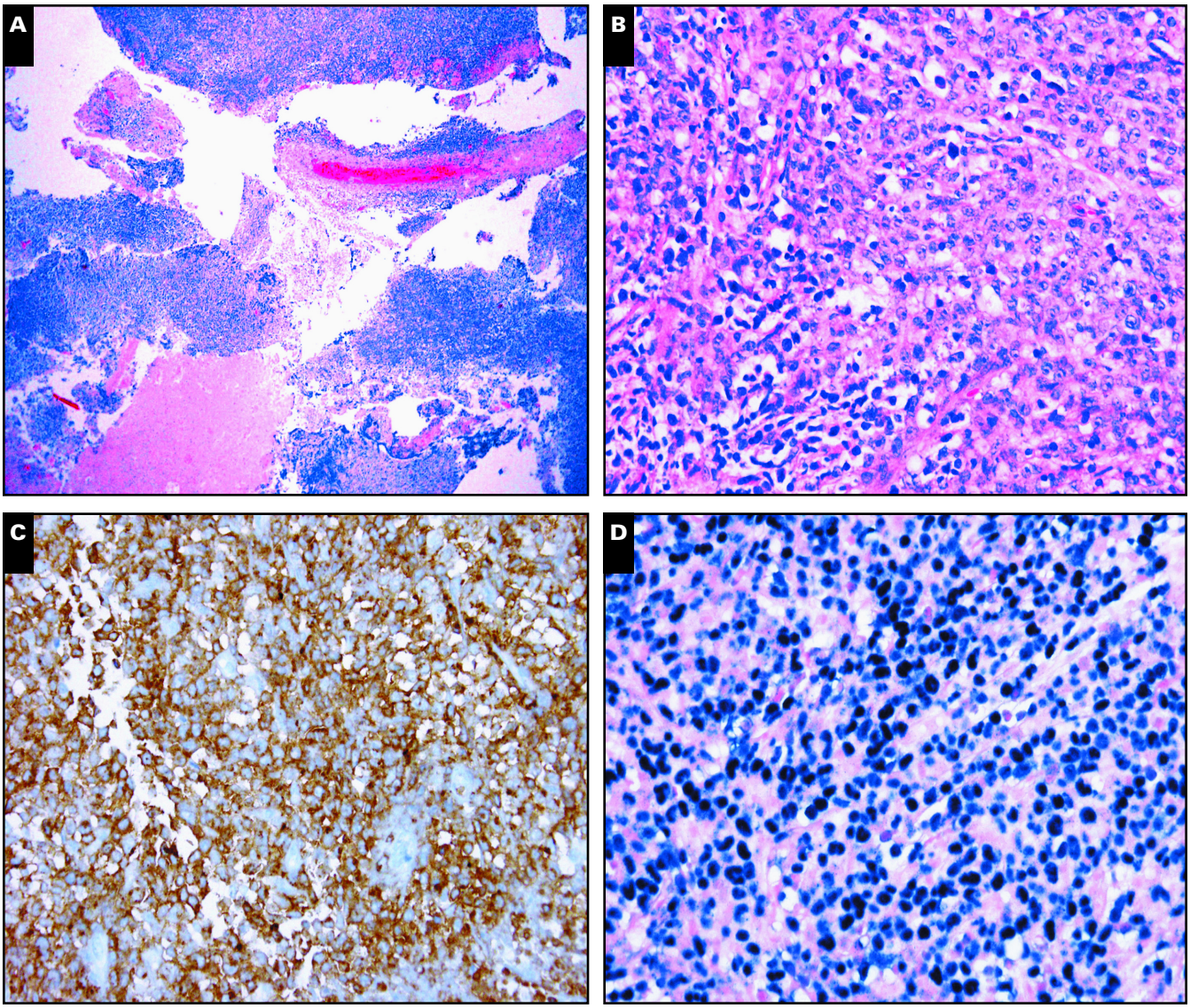

Image 1 Classical manifestations of extranodal natural killer/T-cell lymphoma, nasal type with some unusual features. **A**, The fragmented biopsy specimen shows areas of geographic necrosis (H&E, ×4). **B**, The neoplastic cells are predominantly large. (H&E, ×40). The neoplastic cells are positive for cytoplasmic CD3 (**C**, ×40) and were positive for surface CD3 (by flow cytometry), variably positive for CD30 and cytotoxic granule–associated proteins, and negative for CD56. Epstein-Barr virus small-encoded RNA is demonstrated by in situ hybridization analysis (**D**, ×40). Case contributed by G. Fan.

recrudescing in the setting of immunosuppression following renal transplantation. We have seen similar cases in consultation, as shown **Image 4C** and **Image 4D**. In both cases illustrated, the typical aberrant immunophenotype was demonstrated in the neoplastic cells, but the morphologic findings were so subtle in the initial biopsy specimens that the diagnosis of lymphoma was made only retrospectively, after a second diagnostic biopsy was performed. Such cases with predominantly small lymphocytes can present a diagnostic challenge, requiring EBV studies for clarification.

An important clue to the diagnosis of malignancy in small cell cases is infiltration of bone of the nasal septum; bone infiltration is extremely uncommon in inflammatory conditions and should be considered highly suggestive of the presence of lymphoma (Images 4C and 4D). These cases illustrate that EN-NK/T-NT should be considered in the differential diagnosis of atypical inflammatory infiltrates in the nasal cavity and sinuses. Admixed nonneoplastic inflammatory cells are characteristic of this lymphoma, and if the neoplastic cells are small, these inflammatory cells can make the diagnosis of malignancy problematic, particularly in small biopsy samples.

Immunophenotypic variants of EN-NK/T-NT may also present a diagnostic challenge because the neoplastic cells

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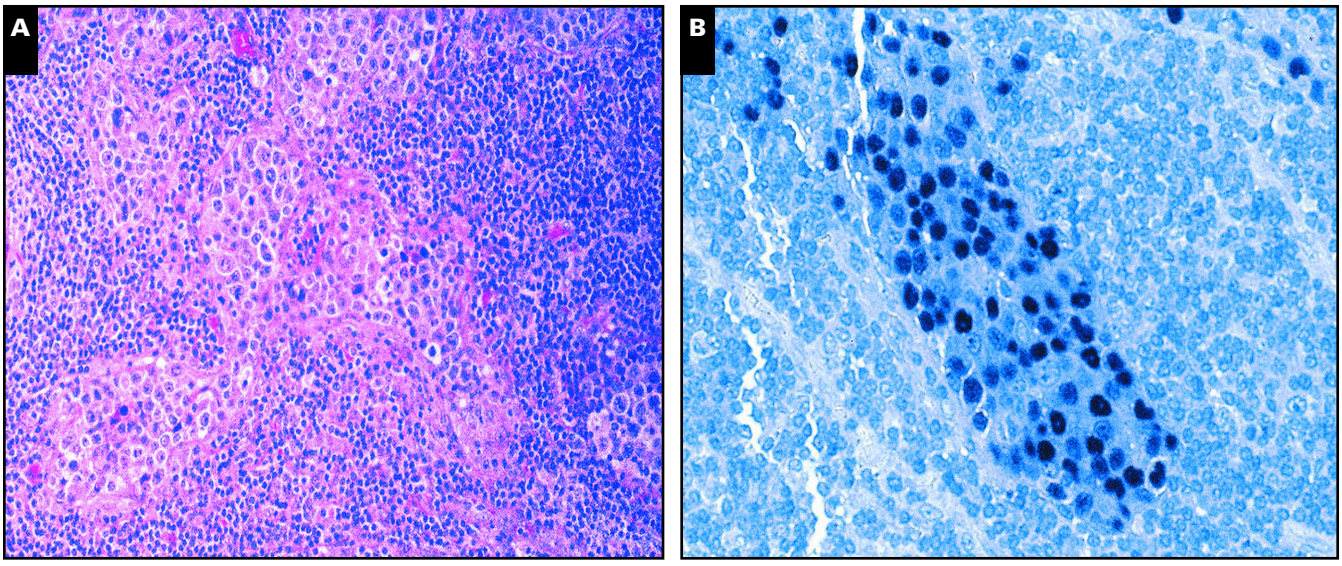

Image 2 Extranodal natural killer (NK)/T-cell lymphoma, nasal type arising in a cervical lymph node of a 27-year-old man. **A**, The tumor displays an unusual sinusoidal pattern of growth (H&E, ×20). **B**, The neoplastic cells are positive for Epstein-Barr virus small-encoded RNA by in situ hybridization (×40). This tumor also displayed a classic NK immunophenotype (CD56+, T-cell–restricted intracellular antigen [TIA-1]+, granzyme+, cytoplasmic CD3+, CD4–, and CD8–). Case contributed by D. Rontogianni.

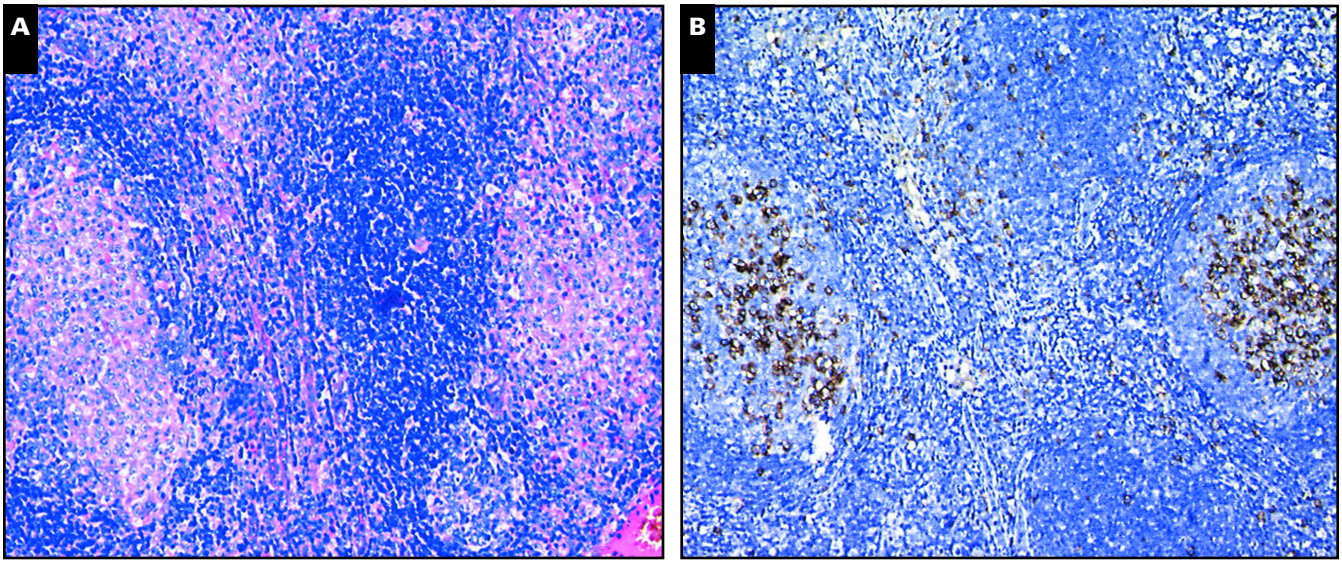

Image 3 Possible case of extranodal natural killer (NK)/T-cell lymphoma, nasal type manifesting in cervical and mediastinal lymph nodes of a 40-year-old woman, showing a "folliculotropic" pattern of infiltration. **A**, The tumor cells are located within expanded follicles (H&E, ×10). CD56 is positive (**B**, ×10), and the tumor had a classic NK phenotype but was negative for Epstein-Barr virus small-encoded RNA. Case contributed by H.K. Müller-Hermelink.

can express CD30 simulating anaplastic large cell lymphoma. Occasional cases with CD30 expression will also show uniform large cell morphologic features (Image 1). However, most large cell variants usually demonstrate a range of cytomorphologic features and variable rather than uniform CD30 staining. These features, combined with the otherwise typical immunophenotype, genetic, and clinical features, will aid in accurate diagnosis.

Small cell variants of EN-NK/T-NT and those with admixed inflammatory cells may mimic a reactive inflammatory process. Staining of these infiltrates for CD56, cytotoxic proteins, and EBER, as well as demonstration of aberrant loss of T-cell antigens such as CD5 and CD7, may help unmask these cases. Some cases of EN-NK/T-NT are composed of large cells and exhibit marked pleomorphism and CD30 expression.

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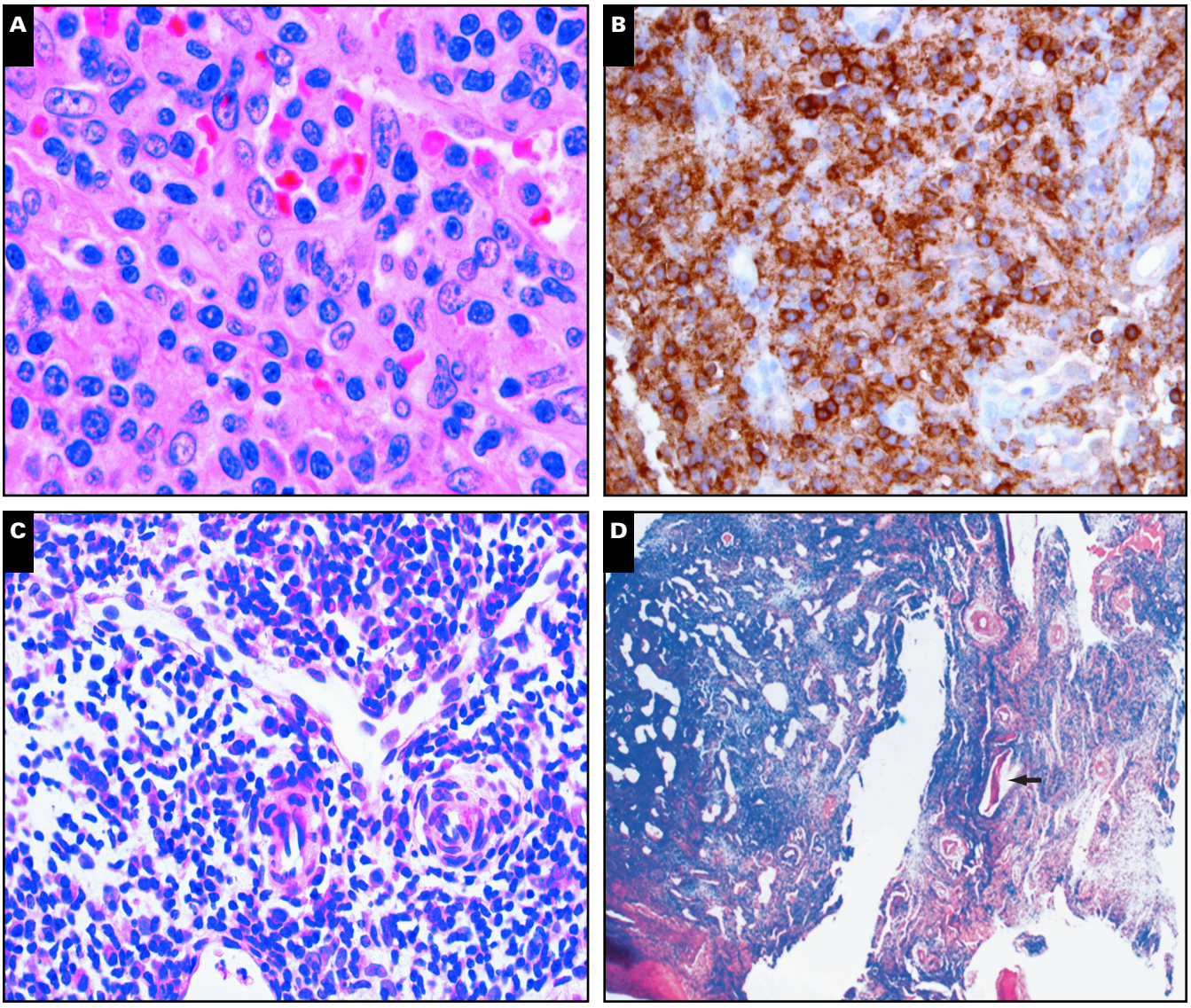

Image 4 Small cell variants of extranodal natural killer (NK)/T-cell lymphoma, nasal type raise the differential diagnosis with a reactive process. **A**, The tumor cells resemble small lymphocytes (H&E, ×100). However, positivity of most of the lymphocytes for CD56 (**B**, ×40) and Epstein-Barr virus small-encoded RNA (EBER; not shown) is characteristic. Case contributed by M. Proytcheva. **C**, Extranodal NK/T-cell lymphoma, nasal type with frequent admixed inflammatory cells (H&E, ×40). Invasion of bone (**D**, H&E, ×2; arrow), in combination with immunohistochemical and EBER studies, helped establish a diagnosis of lymphoma.

How Should Immunophenotypic Aberrancies in Otherwise Typical EN-NK/T-NT Be Handled?

Absence of EBV

Despite the close association of EBV with NK/T-cell lymphomas and leukemias, 3 Workshop cases had many of the features of EN-NK/T-NT yet were EBV–. These neoplasms involved extranodal sites characteristic of EN-NK/T-NT (testis and skin) or unusual sites (female genital tract), but all had the typical immunophenotype of EN-NK/T-NT. In contrast, some EBV– tumors had other features discordant from typical EN-NK/T-NT. For example, 1 EBV– case had nasal involvement and cytotoxic granule protein expression, but also had the atypical feature of expressing CD8. Another EBV– case was nodally based. The Workshop consensus opinion was that EBV– tumors with such discordant features were sufficiently distinct to suggest designation as unclassifiable NK-cell lymphoma. However, no consensus was reached on the classification of otherwise typical EBV– tumors with expression of cytotoxic granule proteins. Of note, the World Health Organization classification of tumors of lymphoid tissues requires both EBV positivity and cytotoxic granule protein expression for a diagnosis of EN-NK/T-NT.[1]

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Absence of CD56 and Evidence of T-Cell Origin

Surface CD3 expression is not seen in normal NK cells or NK-cell neoplasms, which express only the cytoplasmic CD3 ε chain. However, extranodal cytotoxic lymphomas of true T-cell lineage that express surface CD3 constitute a well-recognized subset of EN-NK/T-NT. Of the 4 Workshop cases of nasal-type tumors that expressed surface CD3, 2 were CD8+ and 2 others were CD56–. These cases also exhibited clonal TCR gene rearrangements, supporting the true T-cell origin. These neoplasms have been postulated to arise from an NK-like cytotoxic T cell and, as such, are within the spectrum of EN-NK/T-NT. The classification of tumors that lack expression of CD56 and cytotoxic granule–associated proteins remains problematic. A challenging case submitted to the Workshop was a neoplasm that lacked CD56, TIA-1, and perforin, expressed surface CD3, and had clonal TCR expression but occurred in the pharynx and was EBER+.

B-Cell Marker Expression

Aberrant expression of CD20 has been reported in PTCL unspecified,[14,15] and it is, therefore, not surprising that the Workshop included 2 cases of proposed EN-NK/T-NT that expressed CD20, 1 of which also expressed the additional B-cell marker CD79a **Image 5**. Although it has been proposed that PTCL cases expressing CD20 may represent neoplastic counterparts of the small subpopulation of CD20+ T cells present in healthy people,[15] the significance of B-cell marker expression in NK-cell neoplasms remains uncertain.

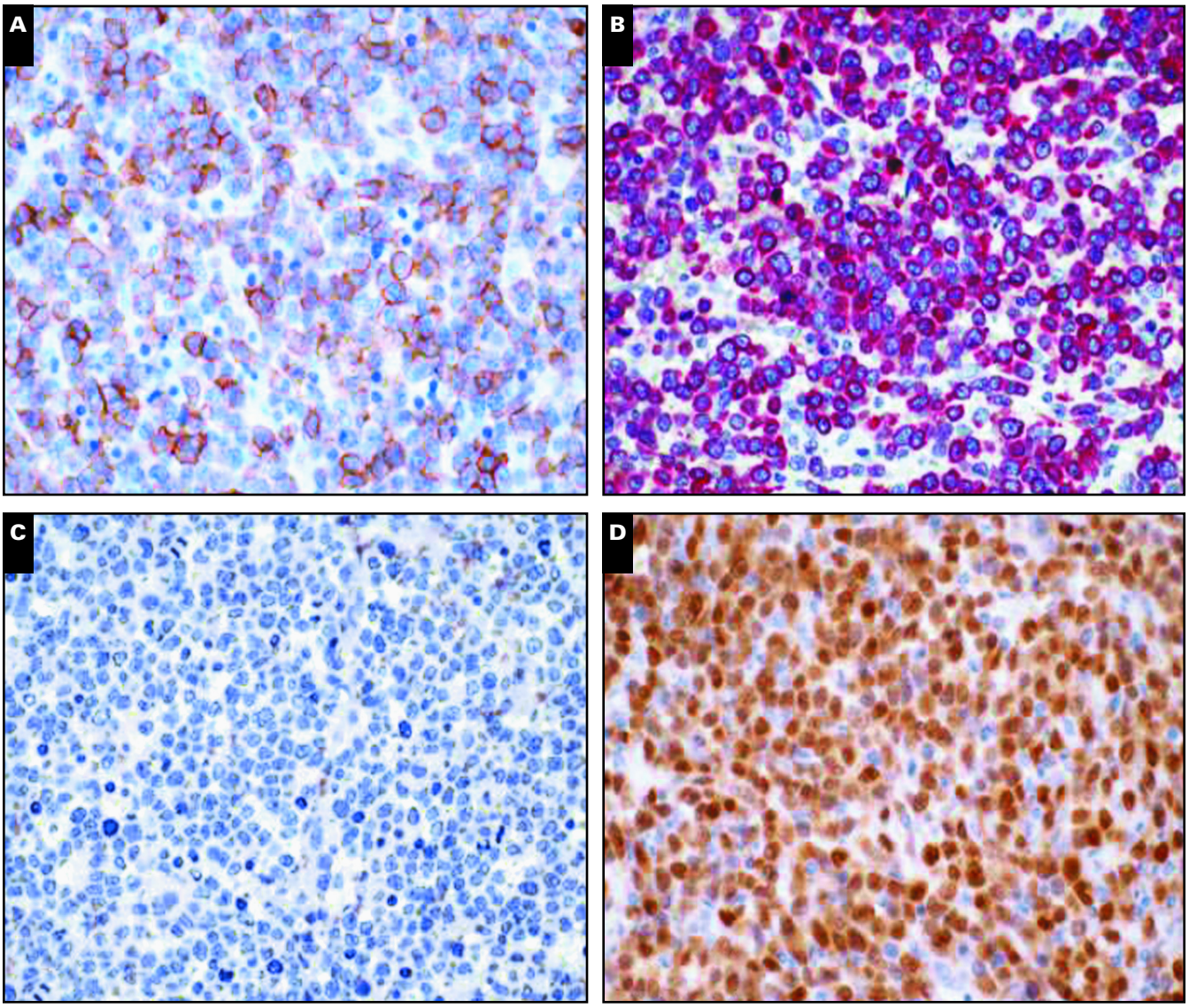

Image 5 Rare cases of extranodal natural killer (NK)/T-cell lymphoma, nasal type may express B-cell markers. This neoplasm involved the female genital tract of a 74-year-old woman. In addition to expressing cytoplasmic CD3, CD56, and cytotoxic granule proteins (not shown), the neoplastic cells were immunoreactive for the B-cell markers CD20 (**A**, ×40), CD79a (**B**, ×40), and MUM1 (**D**, ×40) but were negative for PAX5/BSAP (**C**, ×40). Case contributed by L. Leoncini.

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EBV+ NK/T-cell lymphomas with clinical and morphologic features otherwise typical for EN-NK/T-NT can be classified as such even if they deviate from the classic phenotype (such as expression of CD8 or lack of CD56 expression), provided that they express cytotoxic granule proteins. Demonstration of T-cell origin does not preclude a diagnosis of EN-NK/T-NT, as long as the other features are typical. Classification of EBV– NK/T-cell lymphomas with other discordant features remains controversial; the World Health Organization classification of EN-NK/T-NT requires both EBV positivity and cytotoxic granule protein expression.

Should All Extranodal EBV+ T-Cell Lymphomas Be Grouped With EN-NK/T-NT?

EBV+ T-cell lymphomas have been reported to occur following infectious mononucleosis or chronic active EBV infection[16] and following immunosuppression, including the post-transplantation setting. One Workshop case occurred in a child with a history of immunosuppression and showed a clear T-cell immunophenotype (surface CD3+, CD5+) and was classified as an EBV+ PTCL unspecified. This case may represent T-cell lymphoma arising after acute or chronic EBV infection.[16] Another Workshop case was a CD56+ angioinvasive pulmonary lymphoma with T-cell antigen expression and clonal TCR gene rearrangements that arose in a child who had been treated for several months with cyclophosphamide for hemophagocytic syndrome; it is not clear whether the hemophagocytic syndrome antedated or was secondary to the neoplasm. EBV+ T-cell tumors often are associated with hemophagocytic syndrome and, thus, typically manifest with fever and hepatosplenomegaly.[16]

Although rare, EBV+ T-cell lymphomas related to immunosuppression or PTCL following acute EBV infection seem to be distinct and are best not grouped with EN-NK/T-NT.

What Are the Distinctive Features of Aggressive NK-Cell Leukemia?

In contrast with the broad spectrum of clinical, immunophenotypic, and genotypic features of EN-NK/T-NT, the cases of aggressive NK-cell leukemias presented in the Workshop were more uniform in their manifestations and immunophenotypes: 4 of 5 were EBV+ (often with very high EBV titers demonstrated), and they generally displayed a typical NK phenotype, although 1 case seemed to lack CD56 expression. These cases tended to manifest with B symptoms, hepatosplenomegaly, elevated liver function test results, and cytopenias and were sometimes accompanied by hemophagocytic syndrome **Image 6**.

There are also leukemias with an NK phenotype that lack EBV. In 2 such Workshop cases, the neoplasms were thought to represent transformation, in 1 from a lower-grade NK lymphoma and in the other from a lower-grade NK-cell leukemia of a possible large granular lymphocyte type. Other cases of apparent aggressive NK-cell leukemia arising from lower grade lymphoproliferative diseases have been reported,[17,18] but the EBV status of these reported cases is unknown. The differential diagnosis of aggressive NK leukemias and NK-cell large granular lymphocyte proliferations is discussed elsewhere.

Developing a Diagnostic Toolbox for NK/T-Cell Neoplasms

As illustrated from the wide variety of cases in this Workshop, the minimal diagnostic criteria for EN-NK/T-NT remain controversial, with significant overlap with PTCLs. Important data helpful in correctly classifying these neoplasms include the following (although not all are required to make a diagnosis of EN-NK/T-NT): (1) a thorough clinical history, including knowledge of involvement of the nasal cavity and associated structures, as well as other extranodal sites characteristic of EN-NK/T-NT, such as gastrointestinal tract and skin; (2) immunohistochemical and/or flow cytometric studies to demonstrate expression of CD56 and the lack of expression of T cell–specific antigens (demonstration of the typical surface CD3–, cytoplasmic CD3+ immunophenotype by flow cytometry is also helpful); (3) immunohistochemical analysis to demonstrate expression of cytotoxic granule proteins, such as TIA-1, granzyme, and/or perforin; (4) in situ hybridization for EBER to demonstrate EBV positivity (immunohistochemical analysis for EBV latent membrane protein 1 also may be positive in some tumor cells but is less sensitive than EBER[19,20]); and (5) studies for TCR clonality by polymerase chain reaction–based studies and/or V_β chain clonality assessed by flow cytometry (NK/T-cell neoplasms typically lack clonal TCR gene rearrangements and V_β expression).

Summary

EN-NK/T-NT and aggressive NK-cell leukemia are high-grade neoplasms that are classically EBV+ and display an NK phenotype, lacking clonal TCR gene rearrangements or expression of TCR. As with almost all types of lymphoma and leukemia, the increasing availability and use of ancillary diagnostic techniques such as detailed immunophenotyping and clonality assessment have challenged our definitions by disclosing deviations from the classic descriptions of this entity. Such deviations must be taken into the context of the total diagnostic picture; many of the Workshop cases were thought to be acceptable as EN-NK/T-NT despite lack of totally classic features. One proposed method of handling diagnostic studies in the diagnosis of NK/T-cell lymphoma is shown in **Figure 1**. Nevertheless, classification of neoplasms with overlapping

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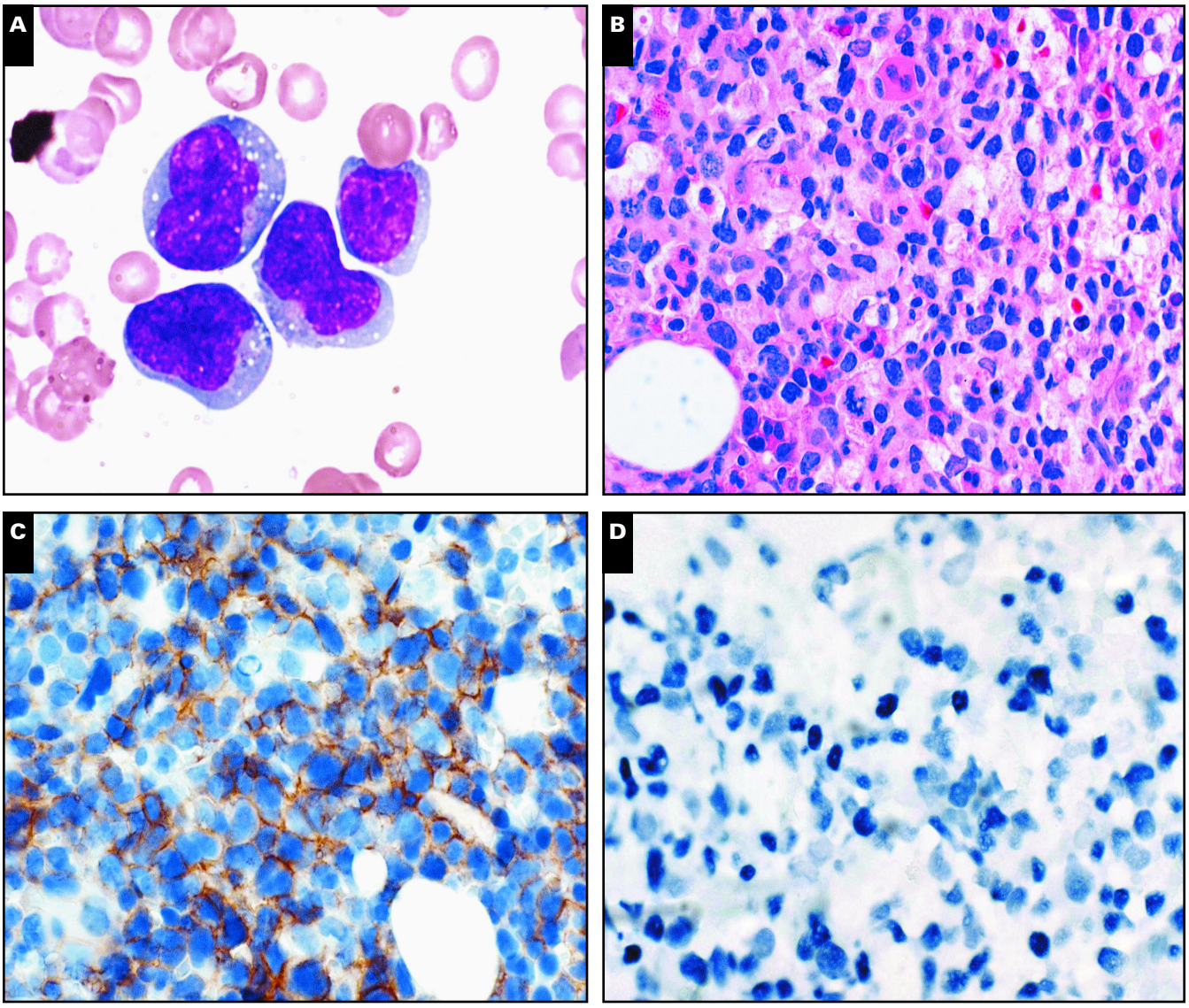

Image 6 Typical case of aggressive natural killer–cell leukemia. **A**, Bone marrow aspirate smear. The neoplastic cells are pleomorphic and may contain azurophilic granules (Wright-Giemsa stain, ×100). **B**, The neoplasm involves bone marrow (H&E, ×40), as well as liver and spleen (not shown). The neoplastic cells express CD56 (**C**, ×40) and are positive for Epstein-Barr virus small-encoded RNA by in situ hybridization (**D**, ×40). Case contributed by Y.H. Ko.

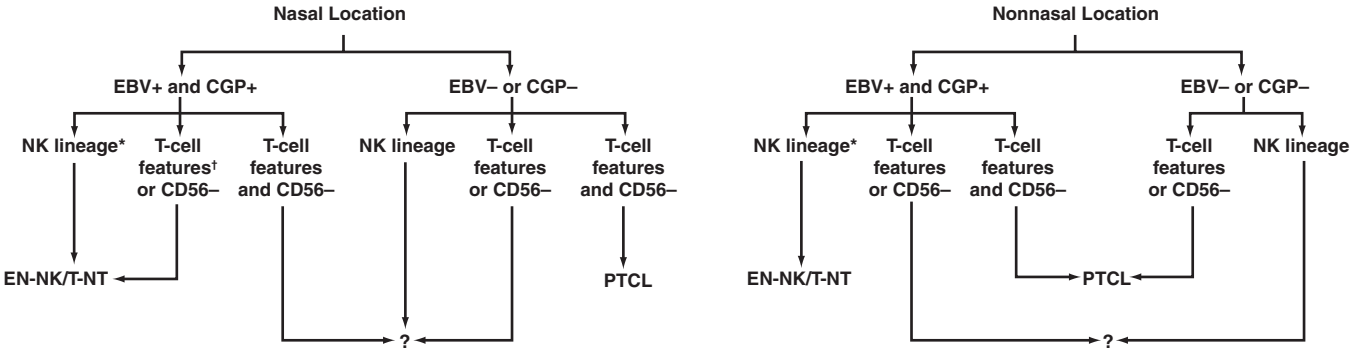

Figure 1 Proposal for classification for natural killer (NK) cell lymphomas, incorporating primary site of involvement, Epstein-Barr virus (EBV) status, and immunophenotype. * NK lineage, germline T-cell receptor (TCR) with surface CD3–/CD5–/CD56+ tumor cells. † T-cell lineage, surface CD3+, CD5+ and/or TCR rearranged. CGP, cytotoxic granule proteins; EN-NK/T-NT, extranodal natural killer (NK)/T-cell lymphoma, nasal type; PTCL, peripheral T-cell lymphoma; ?, unclassifiable NK/T-cell lymphoma.

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features will remain controversial, particularly when EBV is absent. Correlation of pathologic features with the clinical behavior of more of these cases is needed to establish more definitive, widely accepted diagnostic criteria for these rare lymphomas.

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