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REVIEW ARTICLE

Epstein–Barr virus-associated T/natural killer-cell lymphoproliferative disorders

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ABSTRACT

Primary infection with Epstein–Barr virus (EBV) is usually asymptomatic and, in a normal host, EBV remains latent in B cells after primary infection for the remainder of life. Uncommonly, EBV can infect T or natural killer (NK) cells in a person with a defect in innate immunity, and EBV infection can cause unique systemic lymphoproliferative diseases (LPD) of childhood. Primary infection in young children can be complicated by hemophagocytic lymphohistiocytosis or fulminant systemic T-cell LPD of childhood. Uncommonly, patients can develop chronic active EBV (CAEBV) disease-type T/NK LPD, which includes CAEBV infection of the systemic form, hydroa vacciniforme-like T-cell LPD, and mosquito-bite hypersensitivity. The clinical course of CAEBV disease-type T/NK LPD can be smoldering, persistent or progressive, depending on the balance between viral factors and host immunity. Aggressive NK-cell leukemia, hydroa vacciniforme-like T-cell lymphoma, or uncommonly extranodal NK/T-cell lymphoma can develop in children and young adults with CAEBV disease-type T/NK-cell LPD. Extranodal T/NK-cell lymphoma is a disease of adults, and its incidence begins to increase in the third decade and comprises the major subtype of T/NK LPD throughout life. Aggressive NK-cell leukemia and nodal T/NK-cell lymphoma of the elderly are fulminant diseases, and immune senescence may be an important pathogenetic factor. This review describes the current progress in identifying different types of EBV-associated T/NK-cell LPD and includes a brief presentation of data from Korea.

Key words: **Epstein–Barr virus, Korea, lymphoma, lymphoproliferative disease, T/natural killer cell.**

INTRODUCTION

Epstein–Barr virus (EBV) is an oncogenic virus associated with various lymphoproliferative diseases (LPD) of B-, T- or natural killer (NK)-cell lineages. In Western countries, Hodgkin's lymphoma is the most common EBV-associated lymphoma, whereas EBV-associated LPD involving T or NK cells are more prevalent in Asian and Latin American countries. Each entity of EBV-associated malignancy is well defined, and the clinicopathological characteristics are well known. However, the disease definition and terminology, especially for T/NK-cell LPD of childhood, remain controversial.

CLASSIFICATION AND TERMINOLOGY

In the 2008 World Health Organization (WHO) classification, disease entities defined as EBV$^+$ T/NK neoplasm include extranodal NK/T-cell lymphoma (ENKL), aggressive NK-cell leukemia (ANKL) and EBV$^+$ T-cell LPD of childhood.[1] ENKL and ANKL are the prototypes of EBV-associated T/NK malignancy that usually develop in adult patients and take an aggressive clinical course. EBV$^+$ T/NK-cell LPD of childhood encompass T or NK lymphoproliferation across a broad clinical spectrum ranging from indolent to aggressive disease; systemic T-cell LPD of childhood, hydroa vacciniforme (HV)-like lymphoma and mosquito-bite hypersensitivity are included in this category. In the 2012 4th Asian Hematopathology Workshop, the participants raised several issues regarding the diagnostic criteria and terminology for EBV$^+$ T/NK-cell LPD of childhood and adopted the umbrella term "EBV$^+$ T/NK LPD in childhood" to cover the entire spectrum of EBV-associated lesions in childhood, from the reactive to neoplastic processes.

Systemic T/NK-cell LPD of childhood is defined as a fulminant disease associated with the proliferation of polyclonal, oligoclonal or monoclonal T or NK cells, and it includes ANKL in children. The clinical term chronic active EBV (CAEBV) infection is replaced by CAEBV disease-type T/NK LPD to define the nature of the disease clearly. Monoclonal EBV$^+$ T/NK-cell proliferation with the clinical features of CAEBV disease rather than the fulminant course of systemic EBV$^+$ T/NK-cell LPD of childhood is considered CAEBV-type T/NK-cell LPD. HV and HV-like lymphoma are considered to reflect a continuous spectrum of EBV-infected T-cell proliferative diseases involving homing to the skin, and the umbrella term of HV-like T-cell

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LPD has been proposed.[2] The 2012 lymphoma workshop at the European Association for Hematopathology meeting (EAHP) in Barcelona proposed a refined classification for EBV$^+$ T/NK-cell LPD. CAEBV infection is an umbrella term that covers the systemic and cutaneous forms including HV and mosquito-bite hypersensitivity. Systemic T-cell LPD of childhood and ANKL share similar clinical features and belong to the systemic and malignant form of EBV-associated LPD (Histopathology, 2013, in press)[114] (Table 1).

INCIDENCE

Epstein–Barr virus-associated T/NK LPD are prevalent in Asians and in the Native American populations of Mexico, Central America and South America. ENKL accounts for 15% of all cases of non-Hodgkin's lymphoma in the southwest region of China, 6.1% in Korea, 7.8% in Guatemala, 2.6% in Japan, 2.8% in Taiwan, 2.4% in Peru, 2.6% in Chile, and less than 0.1% in Europe and North America.[3–7] In a study from Korea, ENKL was the most common subtype, accounting for 89 of 107 EBV$^+$ T- or NK-type non-Hodgkin's lymphoma cases (83%) followed by ANKL (8.4%).[8] Other disease entities including CAEBV infection-type T/NK LPD are rare, and only sporadic cases or small series have been reported.

In the Korean study, each entity showed a characteristic age distribution.[8] Hemophagocytic lymphohistiocytosis (HLH) is the main subtype of EBV$^+$ LPD in the first decade, although it can develop in any age group. HV-like T-cell LPD occurs in the first and second decades. CAEBV infection of the systemic form can develop at any age but is more commonly diagnosed in the third decade. ANKL shows two age peaks in the third and fifth decades; this distribution is consistent with the data from Japan.[9] ANKL arising in young adults frequently occurs in patients who develop CAEBV, whereas ANKL in middle aged and older adults develops in previously healthy individuals and pursues a rapidly progressive fulminant clinical course. ENKL is a disease of adults, and its incidence begins to increase in the third decade and comprises the major subtype of T/NK LPD throughout life.[8] ENKL in adult patient is usually not associated with CAEBV infection (Fig. 1).

CAEBV DISEASE-TYPE T/NK-CELL LPD

Chronic active EBV infection is clinical term usually applied to chronic systemic illness characterized by high EBV viral load and symptoms such as fever, organomegaly and skin lesions in patients without known immunodeficiency. Systemic CAEBV infection, HV-type T-cell LPD, and mosquito-bite hypersensitivity belong to a continuous spectrum of EBV-associated T/NK LPD with different clinical presentations.

CAEBV infection, systemic

Patients with CAEBV infection show high viral load in the peripheral blood or in the tissues and chronic illness including fever, organomegaly and skin lesions of unknown etiology. Clonal expansion and transformation of EBV-infected T and NK cells are the main pathogenic manifestations. The clinical course depends on the balance between EBV-related factors and host immune function, and can be smoldering, progressive or aggressive. Some patients develop EBV$^+$ T/NK-cell lymphoma/leukemia. From 1998 to 2006, 12 patients in the age range of 1–59 years (median age, 21 years; seven males and five females) were diagnosed with CAEBV disease at Samsung Medical Center, Korea. The common clinical findings included

Table 1. Nomenclature for Epstein–Barr virus$^+$ T-cell and NK-cell lymphoproliferative diseases

Classification of EBV$^+$ T/NK LPD (2012 EAHP Workshop)	Classification of mature T-cell and NK-cell neoplasms (2008 WHO)	Classification for EBV$^+$ T/NK LPD of childhood type (2012 Asian Hematopathology Workshop)
Chronic active EBV infection Systemic (T, NK)		Chronic active EBV disease-type T/NK-cell LPD Polymorphic/polyclonal Polymorphic/monoclonal Monomorphic/monoclonal
	Systemic T-cell LPD of childhood*	
Chronic active EBV infection Hydroa vacciniforme (T)	Hydro vacciniforme-like lymphoma	Hydroa vacciniforme -like T-cell LPD Hydroa vacciniforme Classic type Severe type Hydroa vacciniforme-like T-cell lymphoma
Chronic active EBV infection, Mosquito-bite hypersensitivity (NK)	Mosquito-bite hypersensitivity	Mosquito-bite hypersensitivity
Systemic, malignant EBV$^+$ LPD Aggressive NK-cell leukemia/ lymphoma (NK)	Aggressive NK-cell leukemia	Aggressive NK-cell leukemia
Systemic, malignant EBV$^+$ LPD Systemic EBV$^+$ T-cell LPD	Systemic T-cell LPD of childhood	Systemic EBV$^+$ T/NK-cell LPD of childhood type
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma	Extranodal NK/T-cell lymphoma
Nodal T/NK-cell lymphoma		

*Monoclonal LPD among chronic active EBV infection. EBV, Epstein–Barr virus; LPD, lymphoproliferative diseases; NK, natural killer.

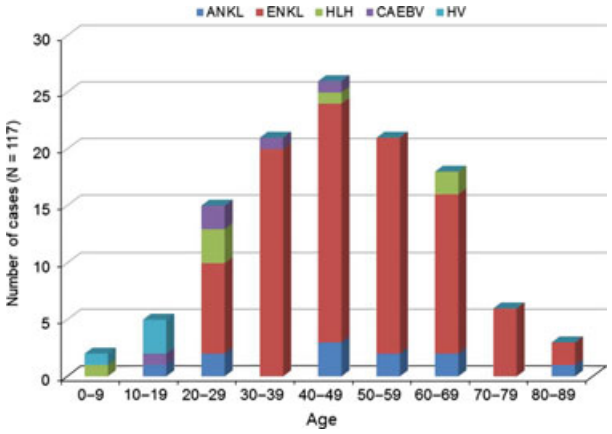

Figure 1. The frequency of subtypes of Epstein–Barr virus (EBV)$^+$ T/natural killer (NK)-cell lymphoproliferative diseases according to age. Primary EBV infection in young children may be complicated by hemophagocytic lymphohistiocytosis or systemic T-cell lymphoproliferative diseases (LPD) of childhood. Uncommonly, patients develop chronic active EBV infection-related diseases including chronic active EBV infection of systemic form, hydroa vacciniforme and mosquito-bite hypersensitivity in early childhood and teenagers. Chronic active EBV infection may progress to aggressive NK-cell leukemia, hydroa vacciniforme-like T-cell lymphoma or uncommonly extranodal NK/T-cell lymphoma in young adults. The incidence of NK/T-cell lymphoma begins to increase from the 20s and forms the major type of EBV-associated lymphoid malignancy throughout life. ANKL, aggressive NK-cell leukemia; CAEBV, chronic active EBV; ENKL, extranodal NK/T-cell lymphoma; HLH, hemophagocytic lymphohistiocytosis; HV, hydroa vacciniforme.

fever (12/12), hepatosplenomegaly and lymphadenopathy (8/12), NK lymphocytosis (5/12), mosquito-bite hypersensitivity (4/12), HV-like eruptions (1/12) and pneumonia (2/12). Some patients presented with bowel perforation, immunoglobulin A nephropathy, chorea or brain infarction. In the mean follow up of 25 months, six patients (50%) died of the disease, four patients (33%) had persistent disease and two (17%) patients improved. The causes of death were infection and organ failure in three patients, T-cell lymphoma in two patients and ANKL in one patient.[8]

Chronic active EBV infection of the T/NK-cell type is always associated with varying degrees of proliferations of T or NK cells.[10–12] Infiltrating cells are usually small and lack cytological atypia, but the degree of histological atypia increases as the disease progresses.[11] Infiltrating cells are mixed CD4$^+$ or CD8$^+$ T, NK, or less commonly B cells. The clonality of EBV and EBV-infected T or NK cells varies and can be polyclonal, oligoclonal or monoclonal. Ohshima *et al.* reported that eight of 48 patients with CAEBV infection exhibited polyclonal infection.[11] In a study from Korea, monoclonality was detected in three of six patients (50%) with CAEBV infection for whom polymerase chain reaction (PCR) analysis for T-cell receptor (TCR) gene rearrangement was successful. Among the three polyclonal patients, one was CD56$^+$ with a skewed killer cell Ig-like receptor phenotype. The median survival was 18 months. Monoclonal CAEBV patients tended to show poorer prognoses.[13]

Because of the continuous spectrum of this disease, Ohshima *et al.*[11] proposed new nomenclature to classify pathological categories. Category A1 is polymorphic LPD with polyclonal proliferation of EBV-infected T or NK cells. Category A2 is polymorphic LPD with monoclonal EBV-infected T or NK cells. Category A3 is monomorphic LPD with monoclonal EBV-infected T or NK cells. Categories A2 and A3 of CAEBV correspond to systemic EBV$^+$ T-cell LPD of childhood in the current WHO classification.[1]

HV-like T-cell LPD (HV and HV-like lymphoma)

Hydroa vacciniforme is a rare cutaneous manifestation of EBV-associated T/NK LPD characterized by blistering photodermatosis in childhood that heals with vacciniforme scarring. HV has been classified into two subtypes based on the clinical characteristics.[14,15] The classic type is a self-limited form of disease characterized by the formation of vesicles on sun-exposed areas and has a benign course that resolves in adolescence or young adulthood.[16] The severe type tends to show more extensive skin lesions, systemic manifestations of CAEBV and peripheral NK lymphocytosis. Approximately half of patients with severe HV progress to NK- or T-cell lymphoma/leukemia.[15,17] Using the new terminology of the WHO classification, severe HV would be considered HV-like lymphoma. In a Korean series of 19 patients, including unpublished cases, the age range was 9–32 years, and 12 were male and seven were female. The clinical course included spontaneous regression in four patients, remission and recurrence in eight patients, and progression to systemic or cutaneous T-cell lymphoma in seven patients (Fig. 2).[13,18–21]

As defined in the 2008 WHO classification, HV-like lymphoma is an EBV$^+$ cutaneous T-cell lymphoma occurring in children that often develops with long-standing HV and is associated with hypersensitivity to mosquito bites and sun sensitivity. The median age in a study from China was 7 years (range, 3–15), including more boys than girls.[22] Patients presented with papulovesicular rash with ulceration and crusting or scarring affecting primarily sun-exposed areas of the skin such as the face.[1,22] Systemic symptoms such as fever, wasting, lymphadenopathy and hepatosplenomegaly are present sometimes.[23,24] In a recent study from Peru, most (11/14) cutaneous EBV$^+$ T- and NK-cell lymphomas in children and young adults belonged to the category of HV-like lymphoma, but three patients had a different clinical presentation that did not involve the face. The mean time of disease before admission to hospital was 69 months (range, 6 months to 31 years). After treatment, only four patients remain alive, although with persistent disease. Ten patients died after a mean follow up of 11.6 months (range, 1–32 months) because of concurrent infections (four patients), disease progression (four patients) or both (two patients).[25]

Histologically, HV is characterized by the presence of dense perivascular lymphocytic infiltration with reticulated degenera-

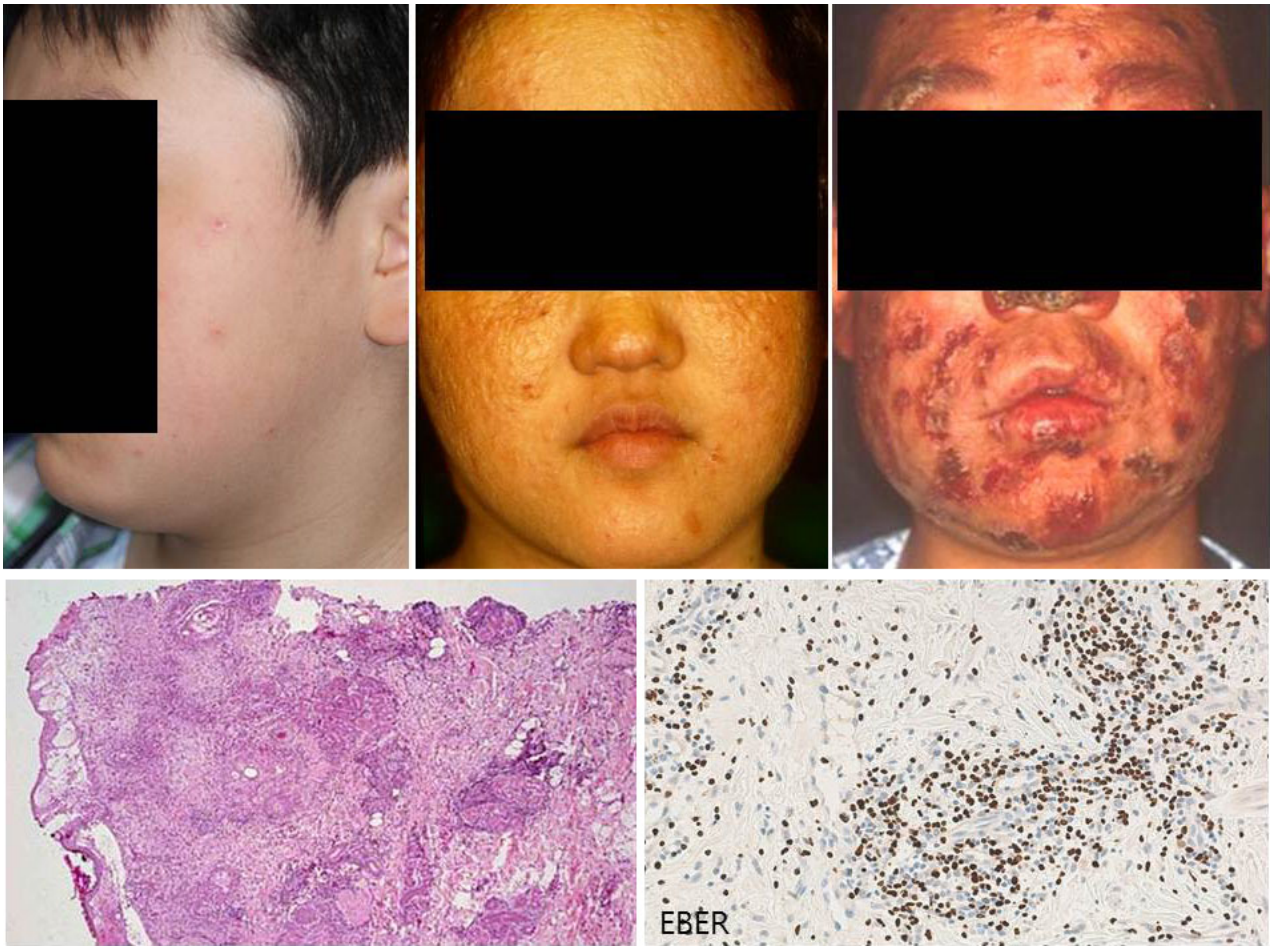

Figure 2. Hydroa vacciniforme-like T-cell lymphoproliferative disease. Case 1 (upper middle). A 7-year-old boy with hydroa vacciniforme, classic type. Case 2 (upper middle). A 12-year-old girl with severe hydroa vacciniforme. She had recurrent skin lesions for 11 years. She developed extranodal natural killer (NK)/T-cell lymphoma involving the larynx at the age of 14. Case 3 (upper right). A 17-year-old boy with hydroa-like T-cell lymphoma. He had recurrent papulonecrotic skin lesion for 7 years. Microscopic finding of case 2 showing hydropic change of the epidermis (left lower; hematoxylin–eosin, original magnification ×10) and heavy infiltration of Epstein–Barr virus (EBV)-infected lymphocytes of the dermis (right lower; EBER *in situ* hybridization, ×200). T-cell receptor gene rearrangement was germ line.

tion of the epidermis. The infiltrating cells are generally small to medium in size without significant atypia.[1] As the disease progresses to overt malignancy, cutaneous lesions become more extensive and deeper, and T-cell monoclonality of the infiltrated cells increases. Differentiation from EBV^+ cutaneous lymphoma of another type should be based on the characteristic vacciniforme cutaneous lesions instead of histopathology. Distinguishing between HV-like lymphoma and HV is often difficult because of overlapping histopathology. EBV and T-cell clonality are found in both types of diseases.

Because HV and HV-like lymphoma constitute a continuous spectrum of disease, an umbrella name of HV-like T-cell LPD of childhood-type was proposed by the Asian Hematopathology Study Group.[2] However, for the purpose of clinical practice, the disease would be better stratified according to the severity and pathological changes. The presence of photosensitivity and symptoms indicating CAEBV infection, such as high viral load in the peripheral blood, clonality of EBV or T cells, deeper dermal infiltration and cellular atypia, can be predictive of poor prognosis in this disease group (Table 2).

Mosquito-bite hypersensitivity

Mosquito-bite hypersensitivity is a cutaneous manifestation of CAEBV infection characterized by intense local cutaneous symptoms including erythema, bullae, ulcers and scar formation, and by systemic symptoms such as fever, lymphadenopathy and liver dysfunction following mosquito bites.[26,27] Although there are exceptional cases of chronic lymphocytic leukemia and mantle cell lymphoma that have occurred without

Table 2. Criteria to stratify hydroa vacciniforme-like T-cell lymphoproliferative disease

Criteria	Hydroa vacciniforme-like lymphoproliferative disease	
	Hydroa vacciniforme	Hydroa vacciniforme-like lymphoma
Photosensitivity	+	−
High viral load in blood	−	+
CAEBV symptom	−	+
EBV clonality	−	+
T-cell clonality	−	+
Depth of infiltrates	Superficial	Deeper
Atypia of infiltrates	−	+

CAEBV; chronic active EBV; EBV, Epstein–Barr virus.

evidence of EBV infection,[28,29] most cases reported so far have been associated with chronic EBV infection syndrome, and up to 33% of patients with CAEBV infection show cutaneous mosquito bit hypersensitivity.[30] Sometimes, hypersensitivity to mosquito bites is the first manifestation of clonal EBV$^+$ NK-cell malignancy.[27]

Most patients with mosquito-bite hypersensitivity are in the first two decades of life, with a median age of 6.7 years in one study.[27] The bite site reveals perivascular mononuclear cell infiltration with an increased number of NK and CD4$^+$ T cells, a considerable proportion of which are positive for EBV.[13,14] In the peripheral blood, NK-cell lymphocytosis is frequently observed, and some of the NK cells carry the EBV genome. In Korea, seven patients were reported in the published work; their age range at admission was 5–46 years (median, 17). All patients were male. Lymphoid neoplasm developed in three patients; one had NK-cell leukemia and two had Hodgkin's lymphoma-like B-cell LPD and marginal zone B-cell lymphoma.[20,31–34]

There is significant overlap of histological findings between HV and insect bite reaction. Spongiotic epidermis and a polymorphous cellular infiltrate throughout the dermis with angiocentricity can be seen in these diseases.[35] The differential diagnosis is based on the clinical findings and identification of EBV-infected lymphocytes in skin biopsy.

SYSTEMIC, MALIGNANT EBV$^+$ T/NK-CELL LPD

Systemic EBV$^+$ T-cell LPD of childhood

Systemic EBV$^+$ T-cell LPD of childhood is a life-threatening illness in children and young adults that is characterized by the clonal proliferation of EBV-infected T cells with an activated cytotoxic phenotype.[1] Similar cases have been reported mainly in Asian countries including Taiwan, Japan and Korea, and they have been described using terms such as fulminant EBV$^+$ LPD of childhood,[36] fatal infectious mononucleosis,[37] fatal EBV-associated HLH[38] and severe CAEBV infection of the T/NK-cell type.[10] The disease occurs mostly in children and young adults after primary EBV infection but can also occur in adults in the setting of CAEBV infection.

Histological changes are characterized by infiltration of hemophagocytic histiocytes and EBV-infected lymphocytes into the bone marrow, liver and spleen. EBV-infected cells usually lack significant atypia. Generally, the typical phenotype is CD2$^+$, CD3$^+$, CD56$^-$ and TIA-1$^+$. Most cases secondary to acute primary EBV infection involve CD8$^+$ cytotoxic T cells, whereas cases in the setting of CAEBV infection involve CD4$^+$ T cells.[1] EBV-infected cells can be CD16$^+$ NK cells, although the incidence of cases with CD16$^+$ NK cells is low.[39–41] This type of disease in children is called "aggressive NK-cell leukemia" and may be regarded as the NK-cell counterpart of systemic EBV$^+$ T-cell LPD of childhood.[2] As such, the pathological category of systemic EBV$^+$ T-cell LPD of childhood has a significant overlap with ANKL in terms of clinical presentation. Therefore, the 2012 EAHP Lymphoma Workshop grouped the two disease entities together into systemic, malignant EBV$^+$ LPD. However, ANKL in adult patients is distinct from systemic EBV$^+$ T-cell LPD of childhood because the former is usually not associated with primary EBV infection and has obvious cytological atypia with significant cytogenetic abnormalities.[2]

Epstein–Barr virus-associated HLH is a clinical disease entity that includes a broad spectrum of illnesses ranging from EBV-associated reactive, polyclonal LPD to neoplastic, monoclonal diseases.[42–44] According to the HLH-2004 criteria,[38] patients must fulfill five of eight criteria: fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent NK-cell activity, hyperferritinemia and high soluble interleukin-2 receptor level. Among the stages of EBV-infected cells, a substantial percentage of patients may progress to monoclonal T-cell LPD during the last evolutional phase, the neoplastic stage, which is equivalent to systemic EBV$^+$ T-cell LPD of childhood of the 2008 WHO classification.[45,46]

The clonality of EBV or EBV-infected T cells in EBV$^+$ HLH has been reported in a few studies in Asia.[13,42,47,48] Using the most recent and advanced technique to study gene rearrangement, the BIOMED-2 protocol, two Asian studies have reported different results. Matsuda *et al.*[48] found that all six Japanese children with HLH exhibited monoclonality. By contrast, among the seven HLH patients reported in the study from Korea, two were clonal and five were polyclonal.[13] Clonal EBV$^+$ HLH is classified as systemic EBV$^+$ T-cell LPD of childhood in the current WHO classification.[1] The distinction between EBV$^+$ HLH and systemic T-cell LPD of childhood is an important issue because most EBV$^+$ HLH cases are treated based on the HLH-2004 regimen with favorable prognosis. Unfortunately, clonality itself has no impact on clinical outcome of HLH patients.[42,47]

In a Korean series, two patients with clonal HLH (systemic T-cell LPD) received chemotherapy but died after 2 and 3 months, respectively. Among the five patients with polyclonal HLH, four received chemotherapy or steroids and died after a median period of 1 month, whereas the one patient treated with the HLH-2004 regimen recovered completely and was alive at the final follow up.[13] Similar to CAEBV-like T/NK LPD and HV-like T-cell LPD, HLH and systemic T-cell LPD seem to reflect a continuous spectrum of EBV-associated systemic LPD of childhood. A clear distinction between the two entities

is difficult and arbitrary, and new terminology encompassing two diseases is needed.

ANKL

Aggressive NK-cell leukemia is characterized by the systemic proliferation of neoplastic NK cells, primarily involving the peripheral blood and bone marrow, and by a rapid progressive clinical course.[1] Less commonly, the spleen and liver, and even the lymph nodes, are affected.[49] Although little is known about the etiology, EBV infection may play a role in the development of clonal lymphoproliferation of NK cells because most aggressive NK-cell leukemia cells are infected with EBV. However, it is unknown how EBV initiates the clonal growth of NK cells. Rarely, patients, especially young patients, also have mosquito-bite hypersensitivity or CAEBV infection.[30,50] By contrast, ANKL in older people usually presents as an acute disease without any underlying EBV-associated LPD. Immune senescence may be related to the pathogenesis of ANKL in older people.

Epstein–Barr virus-negative ANKL has been reported in up to 10% of cases.[51,52] The clinical and pathological findings for EBV^- ANKL are similar to those for EBV^+ ANKL; however, the diagnosis of ANKL in EBV^- neoplasms should be questioned because undifferentiated myeloid neoplasm can mimic NK-cell neoplasm. Laboratory findings include leukocytosis or leukopenia, anemia, thrombocytopenia and increased lactate dehydrogenase concentration. The diagnosis is made when proliferation of large granular lymphocytes (LGL) of the NK-cell type is found in the peripheral blood and bone marrow. Bone marrow shows varying degrees of infiltration and variable cytological characteristics of LGL.[49,51] The infiltration patterns may be massive, focal or subtle with a broad range of cytological features from small to medium-sized lymphocytes without significant atypia to pleomorphic large lymphocytes.[49,52,53] Bone marrow stromal damage, hemophagocytosis and dyserythropoiesis are common findings.[49]

The immunophenotype findings are almost identical to those of ENKL, nasal type: $CD2^+$, $CD3\varepsilon^-/^+$, $CD56^+CD16^-/^+$, $CD7^-/^+$, $CD8^-/^+$, $CD11c^-/^+$, EBV^+, $CD1^-$, surface $CD3^-$ and $CD5^-$.[49,51] Because ENKL, nasal type, may also present as a leukemic phase,[54] it is sometimes difficult or impossible to discriminate between ANKL and the leukemic infiltration of ENKL, nasal type, if current or previous nasal lesions are not present. Surface CD3 negativity by flow cytometric or immunophenotypic analysis and the germ line configurations of T-cell receptor (TCR) genes by TCR rearrangement studies can differentiate T-cell-type LGL leukemia or leukemic infiltration of other T-cell lymphomas from ANKL. ANKL is sometimes indistinguishable from chronic NK-cell lymphocytosis, but the presence of conspicuous nucleoli in NK cells favor the diagnosis of ANKL.[55]

A fulminant clinical course results from liver dysfunction caused by chemokine storm involving FasL, CXCR1, C-C chemokine receptor type 5, interleukin-8, macrophage inflammatory protein (MIP)-1α and MIP-1β, which are produced mainly in ANKL cells or hepatocytes,[56–58] and hemophagocytosis caused by upregulation of tumor necrosis factor-α produced by EBV-infected tumor cells.[59]

Previously, ANKL was thought to be closely related to ENKL, nasal type, because the same chromosomal abnormalities involving 6q.73,74 were found. However, more recent studies using array comparative genomic hybridization (CGH) show recurrent regions of gain of 1q and loss of 7p15.1–p22.3 and 17p13.1, which are characteristic regions in ANKL rather than ENKL, nasal type.[60–62]

ENKL, NASAL TYPE

Extranodal NK/T-cell lymphoma, nasal type, is almost always associated with EBV.[55,63] Most lymphoma cells have clonal episomal EBV, implicating EBV in the pathogenesis. ENKL, nasal type, can be classified into two clinical subgroups: nasal and extranasal. In most cases, the disease occurs in the nasal cavity and upper aerodigestive tract. In a Korean series that analyzed 135 cases of ENKL, the tumors were located in the nasal cavity (51%), non-nasal upper aerodigestive tract (23%), skin (23%), gastrointestinal tract (13%) and soft tissue (7%) (Fig. 3). Age, sex, ethnicity and immunophenotypic profile did not differ between patients with the nasal and extranasal types, but the latter had more adverse clinical features.[64]

Nasal NK/T-cell lymphoma

Nasal NK/T-cell lymphoma located in the nose and the upper airway is the prototype of extranodal NK/T-cell lymphoma, which was originally termed "lethal midline granuloma" because of the midline perforation caused by destruction of the hard palate. It occurs most often in adults (median age, 50 years) and in men. Nasal NK/T-cell lymphoma is uncommon in children. In children, NK/T-cell lymphoma is often associated with mosquito-bite hypersensitivity or other EBV-associated diseases usually in extranasal sites.[65–67]

The cytomorphological spectrum of ENKL, nasal type, is very broad, and the cell sizes can be small, medium, and large and anaplastic.[1] The cytomorphology comprises polymorphous infiltration of small, medium and large atypical lymphocytes accompanied by inflammatory cells. In some cases, the possibility of ENKL, nasal type, can be overlooked because the morphological findings are subtle, and this can lead to the misdiagnosis of a nasal mucosa biopsy as chronic inflammation. EBV-encoded RNA (EBER) *in situ* hybridization is an

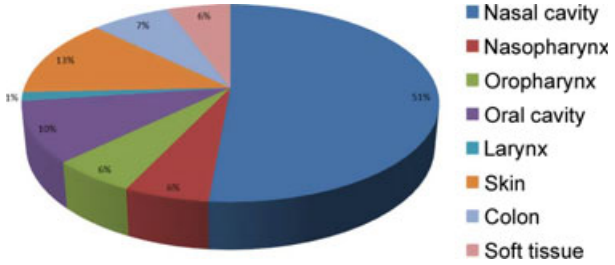

Figure 3. Primary sites for 135 extranodal natural killer (NK)/T-cell lymphomas from Samsung Medical Center, Korea. Nasal cavity and non-nasal upper aerodigestive tract account for 74% of all cases.

important tool for detecting malignancy. However, one should keep in mind that EBV$^+$ B and T lymphocytes can be detected in non-neoplastic nasal mucosa, although the frequency is very rare.[68]

Subtle lymphomatous infiltration in extranasal sites such as the stomach, colon, bone marrow and skin may also be overlooked. In patients with nasal NK/T-cell lymphoma, the gastrointestinal tract may often be involved. Subtle infiltration of lymphoma cells into the stomach or intestine can be overlooked and misdiagnosed as chronic active inflammation.[69] Similarly, minimal lymphomatous infiltrates in bone marrow cannot be identified by morphological analysis alone. The routine use of EBER *in situ* hybridization in bone marrow specimens from patients with ENKL, nasal type, is recommended.[70–72]

The typical immunophenotype is CD2$^+$, CD3ε^+, CD56$^+$, TIA-1$^+$, granzyme B$^+$, perforin$^+$ and EBV$^+$ but surface CD3$^-$, CD57$^-$ and CD16$^-$. Occasionally, the immunophenotype includes CD30$^+$, CD7$^+$ and CD56$^-$. Lymphomas that demonstrate the CD3ε^+CD56$^-$ immunophenotype are also classified as ENKL, nasal type, if the cells are positive for both cytotoxic molecules and EBV.[1]

Extranodal NK/T-cell lymphoma, nasal type, may be of NK- or T-cell origin. Most cases involve germ line configuration in the TCR and Ig genes. The percentage of ENKL, nasal type, reported to be of T-cell origin on the basis of PCR-based research ranges 0–38%.[64,73–79] In one phenotype study, ENKL, nasal type, was reported to be of NK origin (70%), TCR-$\gamma\delta^+$ (5%), TCR-$\alpha\beta^+$ (3%), TCR-$\alpha\beta/\gamma\delta^+$ (1%) and indeterminate (21%).[79]

Despite the rarity of this disease and insufficient biopsy materials, genetic alterations have been studied thoroughly in ENKL, nasal type. Recent array CGH studies have shown that deletion of chromosome 6q (6q21–6q25) is the most frequent site of genomic aberration,[60–62,80–85] and FOXO3 and PRDM1 tumor suppressor genes have been identified in the 6q21–q25 region.[80,81,86,87] Studies also have demonstrated genetic aberrations related to important functions including apoptosis (*FAS*), cell cycle (*TP73*, *CDKN2A*, *CDKN2B*, *CDKN1A*), signaling pathways (*KIT*, *CTNNB1*, *JAK3*), tumor suppressor genes (*TP53*, *PRDM1*, *AIM1*, *FOXO3*, *HACE1*) and oncogenes (*RAS*/*KRAS*/*HRAS*, *MYC*). Several types of aberrations have been noted: mutation, methylation, deletion and amplification.[88] Although the molecular profile of ENKL, nasal type, differs from that of other peripheral T-cell lymphomas,[80,82,89] a subset of extranodal lymphomas derived from $\gamma\delta$ T cells has a very similar molecular signature to that of ENKL, nasal type.[82]

Overall survival is generally poor. Intestinal or non-upper-aerodigestive tract presentation, high stage, bone marrow involvement, high International Prognostic Index score, and lack of radiation dose and field are predictive of poor survival.[1,64,90] The Ki-67 proliferation index was reported to correlate with a shorter disease-free survival.[91] Loss of granzyme B protease inhibitor 9 and cyclooxygenase-2 expression, and decreased quantity of tumor-infiltrating FOXP3$^+$ regulatory T cells correlate with poor prognosis in nasal or upper aerodigestive tract ENKL.[92–94]

Extranasal NK/K-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type, has been reported to occur at other extranodal sites including the skin, soft tissue, gastrointestinal tract, testis, and less frequently, the liver, lung, brain, breast, orbit, tongue, ovary and adrenal gland.[1,95,96] Cutaneous manifestations include erythematous plaques, nodules, tumors, ulcers and vasculitis/panniculitis-like lesions (Fig. 4).[97,98] The primary cutaneous ENKL is clinically less aggressive, more localized, and has a better outcome compared with nasal NK/T-cell lymphoma with secondary spread to the skin.[99] In the gastrointestinal tract, the small intestine is the most frequent site of occurrence.[100] The most common symptoms are abdominal pain, fever, bloody stool, diarrhea and epigastric soreness.[100,101] The main endoscopic patterns are a polypoid or fungating mass, ulceration or multiple small erosions, and diffuse infiltrative lesions with large nodular and sometimes giant folds.[101] Despite aggressive treatment, the prognosis is very poor.[100,101] An initial presentation in the testis is uncommon, although secondary involvement of the testis occurs occasionally, and fewer than 10 cases of primary testis lymphoma have been reported in the published work.[102] Irrespective of treatment, most patients experience a highly aggressive clinical course.[102] Clinical manifestations such as male predominance and age of presentation and the histological findings and the immunophenotype or genotype are also similar to those of nasal ENKL.

NODAL NK/T-CELL LYMPHOMA

The recent 2008 WHO classification of hematopoietic and lymphoid neoplasms recognized two disease entities arising from mature NK/T cells including ENKL, nasal type, and ANKL. ENKL, nasal type, almost always has an extranodal presentation.[1] Although it may be accompanied by secondary lymph node involvement (30.3–55.6%),[103–106] the isolated nodal involvement of NK/T-cell lymphoma is extremely rare. Only approximately 21 cases have been described in the English-language published work.[74,107–111] At present, nodal NK/T-cell lymphoma is not considered a distinct disease entity in the WHO classification.

Clinically, most patients are male (18/21), with an age range of 23–88 years, although most are older. Nodal involvement without nasopharyngeal lesions is observed consistently at presentation. Cervical or axillary lymph nodes are the most frequently affected sites, and many cases are characterized by an advanced clinical stage (III–IV). Some patients also have HIV, hepatitis C virus or hepatitis B virus infection.[107,112] Histopathological findings show diffuse monotonous or polymorphic infiltration of small to large atypical lymphocytes, reminiscent of nodal cytotoxic T-cell lymphomas.[109,111] Immunophenotype findings are typically CD2$^+$, CD3ε^+, CD8$^+$, CD56$^{+/-}$, TIA-1$^+$, granzyme B$^+$, perforin$^+$ and EBV$^+$.[107,111] Monoclonal TCRγ gene rearrangement was demonstrated in some (6/17) patients whose clonality could be analyzed, indicating a cytotoxic T-cell lineage in a subset of nodal NK/T-cell lym-

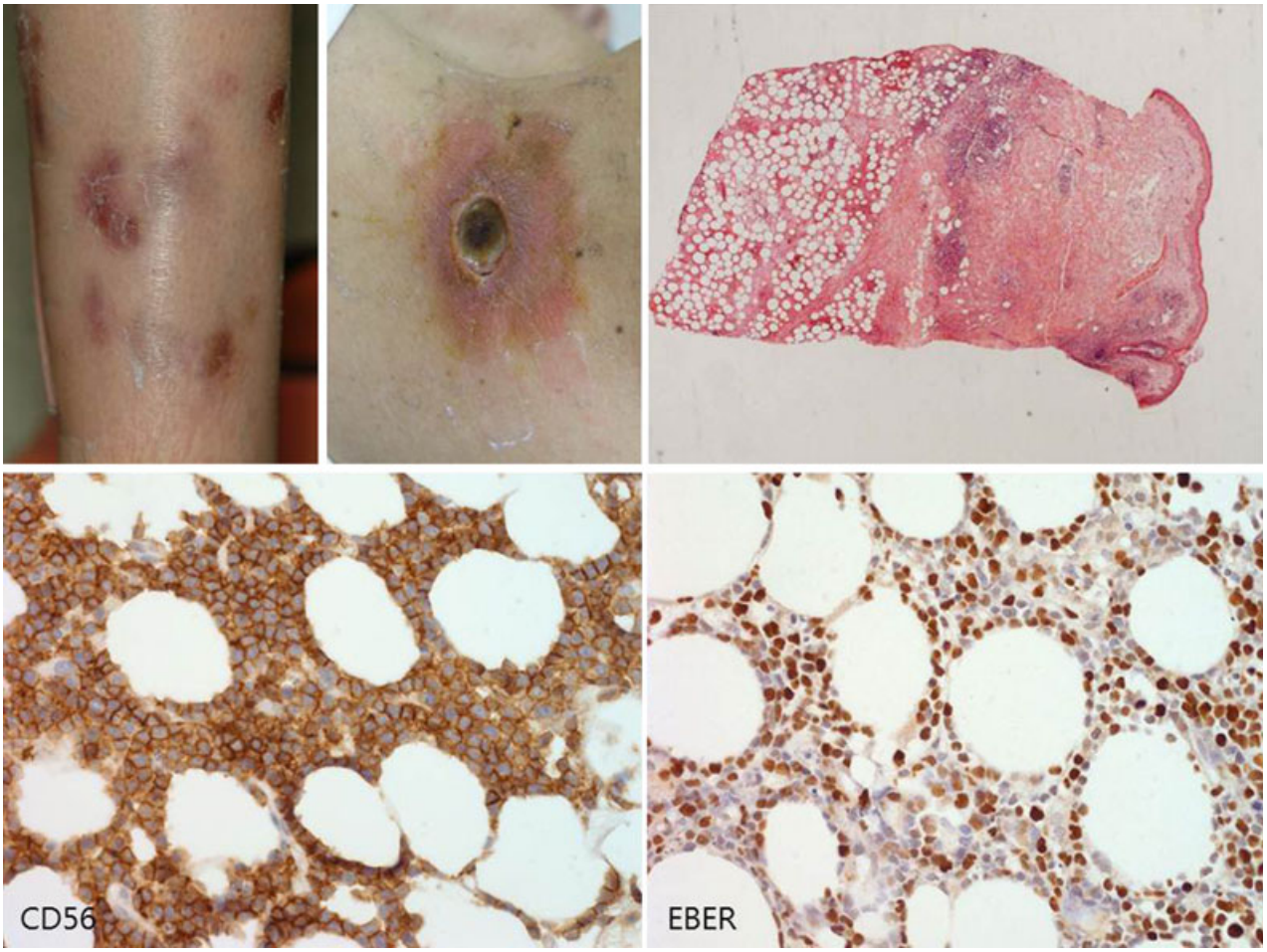

Figure 4. Primary cutaneous extranodal natural killer (NK)/T-cell lymphoma. The entire dermis and subcutaneous tissue are involved (hematoxylin–eosin, original magnification ×10). Tumor cells express CD3, CD56 (lower left) and granzyme B. Virtually all tumor cells are positive for EBER *in situ* hybridization (lower right).

phoma.[74,108,109,111,113] The clinical outcome is dismal. Of the 17 patients with available follow-up data, all died of lymphoma with systemic lymphomatous involvement or hemophagocytic syndrome.[107–109,111]

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