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T- and NK-Cell Lymphomas and Systemic Lymphoproliferative Disorders and the Immunodeficiency Setting

2015 SH/EAHP Workshop Report—Part 4

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Key Words: Iatrogenic immunodeficiency; Posttransplant lymphoproliferative disorder; T-cell lymphoma; NK-cell lymphoma; Systemic T- or NK-cell lymphoma of childhood

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ABSTRACT

Objectives: *The 2015 Workshop of the Society for Hematopathology/European Association for Haematopathology aimed to review immunodeficiency-related T- and natural killer (NK)–cell lymphoproliferations.*

Methods: *The Workshop Panel reviewed 88 T- or NK-cell lymphoproliferations and rendered consensus diagnoses.*

Results: *Hyperplasias of T-cell subsets may be clonal; retained architecture and the clinical setting support a benign diagnosis. Specific associations include hepatosplenic T-cell lymphoma with iatrogenic immunosuppression and breast implants with an indolent variant of anaplastic large cell lymphoma. Epstein-Barr virus (EBV)–positive T-cell lymphomas rarely occur in the acquired immunodeficiency setting. Systemic T- and NK-cell lymphoma of childhood overlaps with chronic active EBV and reversible hemophagocytic lymphohistiocytosis-related T-cell lymphoproliferations.*

Conclusions: *Immunodeficiencies predispose to T-cell hyperplasias, which must not be overdiagnosed as lymphoma. Many T-cell lymphomas in the immunodeficiency setting are likely coincidental, with specific exceptions. Systemic T- or NK-cell lymphomas are part of a spectrum of EBV+ T or NK lymphoproliferations and can present in the acquired immunodeficiency setting.*

Upon completion of this activity you will be able to:

- describe the range of T- and natural killer (NK)–cell lymphoproliferative disorders arising in immunodeficiency settings and secondary B-cell proliferations occurring in the setting of T-cell lymphoma.
- describe the presentations of systemic Epstein-Barr virus–positive T- and NK-cell lymphoproliferative disorders and their relationship with hemophagocytic lymphohistiocytosis.

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Drs Dita Gratzinger, Daphne de Jong, and Elaine Jaffe chaired the Workshop Sessions on T- and natural killer (NK)–cell lymphomas and systemic lymphoproliferative disorders (LPDs) and the immunodeficiency setting, as well as functioned as the co-lead authors of this manuscript. In contrast to the well-developed framework for immunodeficiency-related B-cell LPDs covered in parts 1, 2, and 3 of the Workshop Report, current understanding of the relationship of T- and NK-cell lymphomas and LPDs to immunodeficiency is less overarching and more specific to particular diagnostic and immunodeficiency entities.

Table 1
Spectrum of T- and NK-Cell Lymphoproliferative Disorders in Immunodeficiency States[a]

Characteristic	Nodal HP	Nodal T-Cell Lymphomas	Extranodal HP	Extranodal Lymphomas	Systemic T or NK Disorders
Posttransplant		PTCL (1,[b] 9) ALCL (3) AITL (1, 1B)	γδT, PB (1)	MEITL (2) PC ALCL (1) ATLL (1) ENKT (1[b])	CAEBV (1[b]) SETCL (1[b])
Iatrogenic/ autoimmune	FHT (1) IMT (1) GranT (1)	PTCL (1,[b] 2) AITL (1B)	γδT, BM (1) LGL, PB (1)	HSTCL (4) PC ALCL (1[b]) ENKT (1[b])	SETCL (1[b]) HLH-T (1[b])
HIV		ALCL (1) PTCL (2[b])			SETCL (1[b])
Primary	CytoT (1) γδT (1) DNT (1)		GranT, skin (2) CytoT, liver (1) Clonal, BM (1)	T-PLL (1) T-ALL (1)	
Other or unknown		PTCL (3,[b] 1, 1B[b]) AITL (1B[b]) ALCL (1)	γδT, spleen (1) γδT, PB (1)	BI ALCL (3) ATLL (2) PC ALCL (1[b]) ENKT (4[b]) ANKL (4[b])	SETCL (7[b]) CAEBV (3[b]) HLH-T (1[b]) HV (1[b])

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ANKL, aggressive NK leukemia; ATLL, adult T-cell leukemia/lymphoma; BI ALCL, breast implant–associated anaplastic large cell lymphoma; BM, bone marrow; CAEBV, chronic active Epstein-Barr virus (EBV) infection; CytoT, cytotoxic T cells; DNT, double-negative α/β T cells; ENKT, extranodal NK/T-cell lymphoma, nasal type; FHT, follicular helper T; GranT, granulomatous T-cell infiltrate; HIV, human immunodeficiency virus; HLH-T, hemophagocytic lymphohistiocytosis–associated T-cell infiltrate; HP, hyperplasia; HSTCL, hepatosplenic T-cell lymphoma; HV, hydroa vacciniforme–like lymphoproliferative disorder (World Health Organization [WHO] 2016 update), previously hydroa vacciniforme–like lymphoma; IMT, immunoblastic T cells; LGL, large granular lymphocyte; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma (WHO 2016 update), previously enteropathy-associated T-cell lymphoma type 2; NK, natural killer; PB, peripheral blood; PC ALCL, primary cutaneous anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma; SETCL, systemic EBV+ T-cell lymphoma of childhood (WHO 2016 update), previously systemic EBV+ T-cell lymphoproliferative disorder of childhood; T-ALL, T-cell acute lymphoblastic leukemia/lymphoma; T-PLL, T-cell prolymphocytic leukemia.
[a]Numbers in parentheses indicated the number of cases submitted. B (in parentheses) indicated secondary B-cell proliferation.
[b]EBV+.

Overarching models for immunodeficiency-related T- and NK-cell proliferations in analogy to those proposed for B-cell proliferations are currently unsupported by evidence. Based on the submitted cases, the workshop aimed to describe the spectrum of immunodeficiency-related T- and NK-cell proliferations vs coincidental lymphomas and to discuss (reversible) hyperplasias with a focus on describing pitfalls for overdiagnosis. The workshop accepted 88 submissions of T and NK LPDs, which are presented in **Table 1** according to their category of underlying immunodeficiency or dysregulation, if known. T and NK LPDs and their relationship to immune deficiency and dysregulation will be discussed in the first section; the systemic Epstein-Barr virus (EBV)–positive T and NK LPDs/lymphomas are discussed in part 2.[1] Primary immunodeficiency-related lymphomas are discussed separately in part 5.[2]

Spectrum of T and NK Lymphoproliferative Disorders in Immunodeficiency States

Table 1 lists the T and NK LPDs accepted to the workshop in the various clinical immunodeficiency groups and shows the broad spectrum of nodal and extranodal disease and T and NK disease classes. The panel came to a consensus diagnosis on each case based on the clinical information available, which generally included age, associated immunodeficiency, EBV status of the lymphoproliferation, immunophenotype, and, in many cases, clonality studies. The large group of systemic EBV+ T- and NK-cell LPDs is discussed separately in the second section. Peripheral T-cell lymphoma not otherwise specified (PTCL NOS) is the most frequent diagnosis, reflecting a current lack of tools to better classify what is undoubtedly a heterogeneous group; examples of most categories of T and NK lymphoma recognized by the World Health Organization (WHO) were received. Of perhaps greater interest is the little-explored category of immunodeficiency-associated T-cell hyperplasias, whether nodal or extranodal; indolent NK proliferations have been recognized outside of the immunodeficiency setting.

In the B-cell compartment, there is a clear-cut link between immunodeficiency and increased risk of predominantly EBV-driven B-cell LPDs, which exhibit a broad range in biological and clinical features in diverse settings of immune dysfunction. These range from so-called early lesions (now called *nondestructive*) through polymorphic LPDs through intermediate- and high-grade lymphomas across posttransplant, iatrogenic/autoimmune, primary immunodeficiency, and other immune dysregulation settings. It is unclear whether T and NK LPDs in the immunodeficiency setting can be fit to a

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comparable model of hyperplasias, lymphoproliferations of varied malignant potential, and overt lymphomas, and there is in particular very little information about "early" nonmalignant T and/or NK lymphoproliferations in immunodeficiency settings. Complicating this issue is the reciprocal link between T-cell lymphomas or T/NK expansions and immune dysregulation; the lymphoma itself may be the cause for immune dysregulation as is most well known in the case of angioimmunoblastic T-cell lymphoma.[3,4]

It is similarly difficult to fit the role of EBV as it is understood in the classification of B-cell immunodeficiency-related LPD to T- and NK-cell LPD in the immunodeficiency setting. In contrast to B-cell proliferations, which have variable EBV status outside the immune deficiency context, EBV status is definitional for specific T and NK lymphomas (systemic EBV+ T-cell lymphoma of childhood; EBV+ extranodal NK/T-cell lymphoma, nasal type; aggressive NK leukemia), irrespective of an immune deficiency context. EBV status alone cannot be used as an argument to support a causative role for associated immunodeficiency in NK/T-cell lymphoma. In each case, the category of associated immunosuppression should be noted; future studies may note differences in the frequency and clinicopathologic course of NK/T-cell lymphoma in specific immunosuppressive settings. Response to reduction in immunosuppression, if present, would argue for a causative association of iatrogenic immunodeficiency; in cases of noniatrogenic immunosuppression, the association should be noted, but causality may not be ascertainable at this time.

While so-called early immunodeficiency-related B-cell lesions are recognized by virtue of their EBV+ status, hyperplasias and expansions of T-cell subsets in states of immunodeficiency or dysregulation are generally EBV–, as seen among the workshop cases (Table 1). Therefore, outside very few settings of specific and well-defined associations as discussed below, it is unclear whether most or only a small subset of T-cell lymphomas occurring in the immunodeficiency setting are etiologically linked to the immunosuppression. Indeed, for some EBV– T-cell lymphomas, the temporal relationship may well be incidental. Probably coincidental examples in the posttransplant setting include epitheliotropic intestinal T-cell lymphoma (formerly enteropathy associated T-cell lymphoma type II) (SH2015-12, submitted by Dr Inamdar and colleagues; SH2015-181, submitted by Dr Ru), adult T-cell lymphoma/leukemia (SH2015-366, submitted by Dr Dudley and colleagues), and ALK+ anaplastic large cell lymphoma (SH2015-413, submitted by Drs de Leval, Bisig, and Pascual). By contrast, Dr Cook submitted an EBV+ primary cutaneous anaplastic large cell lymphoma (ALCL) in an iatrogenic immunodeficiency state (SH2015-208); EBV is only rarely if ever described in ALCL, leaving the possibility of an etiologic relationship open. A compelling case for an etiologic relationship can also be made for a case of angioimmunoblastic T-cell lymphoma (AITL) occurring in an 8-year-old boy[5] in the posttransplant setting. AITL is otherwise exceedingly rare in children. The histology of case SH2015-225, submitted by Drs Kurzer and Kraus, is entirely consistent with AITL, and **Image 1A** shows classic findings of marked paracortical expansion with scattered larger cells, admixed eosinophils, and prominent arborizing high endothelial venules. Immunohistochemistry demonstrates a follicular helper T-cell phenotype and highlights the aberrant expansion of the follicular dendritic cell meshworks.

T-Cell Lymphomas Arising in Altered Immune States

Two specific associations between immunodeficiency or aberrant immune stimulation state and a specific type of T-cell proliferation have been reported.

1. *Iatrogenic immunodeficiency and hepatosplenic T-cell lymphoma (HSTCL):* We received four cases of HSTCL,[6] all γδ T cell in immunophenotype and all associated with iatrogenic immunosuppression in the setting of autoimmune/rheumatologic disease. Drs Sajid and Goradia submitted case SH2015-162 of HSCTL in a patient with rheumatoid arthritis treated with prednisone, methotrexate, and a tumor necrosis factor α (TNFα) inhibitor; Drs Tousseyn and Wlodarska submitted case SH2015-336 of HSCTL in a patient with Crohn disease treated with cyclosporine; Drs Wilson, Rosen, and Pitchford submitted case SH2015-212 of HSCTL in a patient with sarcoidosis treated with azathioprine, TNFα inhibitor, and methotrexate; and Drs Low, Chan, and Weisenburger submitted case SH2015-270 of HSCTL in a patient with ulcerative colitis treated with 6-mercaptopurine, steroids, and TNFα inhibitor.

Case SH2015-336 is a prototypical case of iatrogenic inflammatory disease–related HSTCL **Image 1B**: the patient had been chronically treated with cyclosporine for Crohn disease for more than 5 years when he presented with pancytopenia, fever, and splenomegaly. The splenic red pulp (Image 1A) and bone marrow sinusoids were infiltrated and expanded by an atypical T-cell infiltrate with a typical clonal cytogenetic abnormality, i(7)(q10). The WHO designation for HSCTL does not include the γδ designation in recognition of the similar clinical and genetic phenotype of the αβ variant.[7]

Long-term exposure to thiopurines with or without TNFα inhibitor has been recognized as a risk factor for development of HSTCL in young men with inflammatory bowel disease.[8] Rare cases have been reported in the setting of rheumatoid arthritis treated with combination immunosuppression, including TNFα inhibitors.[9] The unique sarcoidosis-associated HSTCL also treated with thiopurine and TNFα inhibitor shows that the spectrum of underlying autoimmune disorders will likely broaden.

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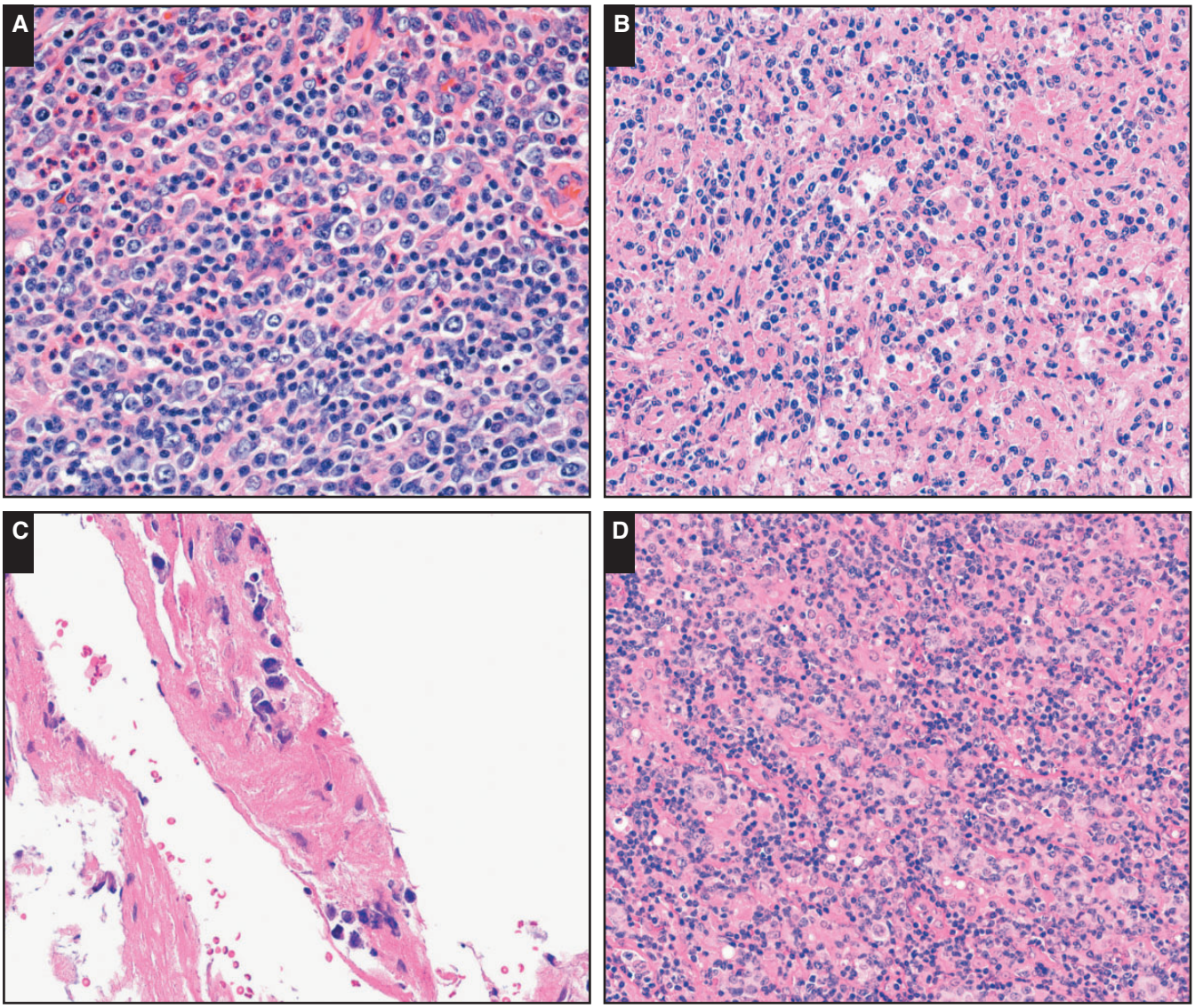

Image 1 T-cell lymphomas and immunodeficiency. (**A**) SH2015-225: angioimmunoblastic T-cell lymphoma in a child in the posttransplant setting showing marked paracortical expansion with scattered larger cells, admixed eosinophils, and prominent arborizing high endothelial venules. (**B**) SH2015-336: γδ hepatosplenic T-cell lymphoma in a patient with Crohn disease chronically treated with cyclosporine. Note the monomorphous lymphoid infiltrate expanding the splenic red pulp. (**C**) SH2015-126 is a prototypical case of a non-mass-forming, noninvasive breast implant–related anaplastic large cell lymphoma with an excellent prognosis after complete surgical excision despite markedly pleomorphic cytologic features. (**D**) SH2015-217: secondary Epstein-Barr virus–positive B-cell proliferation resembling a Hodgkin-like immunodeficiency-related lymphoproliferative disorder in the background of a follicular helper-type T-cell lymphoma. (**A**, H&E, ×40; **B**-**D**, H&E, ×20)

2. *Breast implant–associated ALCL, seroma type:* in part 2, we have discussed several morphologically pleomorphic but clinically indolent EBV+ large B-cell proliferations at sequestered sites, such as cardiac myxomas, likely associated with some degree of chronic trauma or inflammation and (local) immune dysregulation. Similarly, despite alarming cytologic features, noninvasive ALCL involving seroma fluid sequestered between a breast implant and its reactive fibrous capsule[10] behaves in a remarkably indolent manner and may often be treated with complete capsulectomy alone.[11,12] ALCL presenting with a mass or invasion may behave more aggressively.[13] The distinct clinicopathologic behavior of breast implant–associated ALCL from other ALK– anaplastic large cell lymphomas has led to its recognition as a provisional entity in the 2016 update to the WHO classification.[7] Case SH2015-126 submitted by Dr Michel is prototypical; the patient developed enlargement and inflammation of the breast and a periprosthetic fluid collection 4 years after placement of the prosthesis. Staging revealed no

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mass lesion, and prosthesis removal with capsulectomy resulted in an excellent outcome with no disease recurrence. Pathologic examination showed characteristic anaplastic cells within a cell block from the fluid collection and rare noninfiltrative nests of large cells associated with the capsule **Image 1C**.

Lymphoma Itself as a Basis for Immune Dysfunction

AITL prototypically causes autoimmunity and immune dysregulation with frequent secondary B-cell proliferations.[14] Common features of immune dysregulation in AITL include skin rashes, hypergammaglobulinemia, and autoimmune hemolytic anemia[15]; less common is a symmetric inflammatory polyarthritis that can be misdiagnosed as a primary rheumatologic disorder.[16] Secondary B-cell proliferations are also seen in other T-cell lymphomas, particularly those with a follicular helper T-cell immunophenotype.[17-19] The molecular, phenotypic, and pathophysiologic similarities among T-cell lymphomas with this phenotype[20] have in fact prompted recognition of a new umbrella category of T-cell lymphomas with a T follicular helper (TFH) phenotype that include nodal PTCL with a TFH phenotype, follicular T-cell lymphoma (formerly PTCL NOS, follicular variant), and AITL.[7]

Secondary B-cell lymphoproliferations can be EBV+ or EBV– and may resemble Hodgkin-like, centroblast-like, or polymorphous proliferations that are highly reminiscent of those seen in the spectrum of B-cell proliferations in the immune deficiency setting resembling classical Hodgkin lymphoma and T-cell–rich B-cell lymphoma, as discussed in part 2. We received four cases of T-cell lymphomas with secondary B-cell proliferations; of these, two were AITLs (SH2015-90, submitted by Drs Wu and Tan, with an EBV+ secondary B-cell proliferation, and SH2015-234, submitted by Drs Hoffman and Ohgami, with an EBV– secondary B-cell proliferation), and two were PTCLs with a TFH cell phenotype (SH2015-217, submitted by Dr Xu and colleagues, with an EBV+ secondary B-cell proliferation, and SH2015-225, submitted by Drs Kurzer and Kraus, with an EBV– secondary B-cell proliferation). The secondary B-cell proliferation can be more prominent than the underlying T-cell lymphoma, raising the potential for misdiagnosis. Case SH2015-217 **Image 1D** has a histologic picture dominated by Hodgkin/Reed Sternberg cells that are CD45–, CD30+, CD15+, PAX5 dim immunophenotype with variable CD20, mimicking classical Hodgkin lymphoma. The background atypical T-cell infiltrate is much less conspicuous histologically, and the diagnosis of an underlying follicular T-cell lymphoma requires a combination of careful histologic review to identify the diffuse background infiltrate with a TFH pattern of antigen expression, the range in cell size of the Hodgkin-like cells from small to large, and confirmatory clonal T-cell gene rearrangement studies.

Nonmalignant T Proliferations in Immunodeficiency and Immune Dysregulation States

A spectrum of nonovertly malignant T-cell proliferations in immunodeficiency and immune dysregulation states and infectious diseases was discussed in the workshop. The problems in this area focus on obvious mimics of malignancy but also on hyperplasias and atypical hyperplasias that may or may not represent precursor lesions of immunodeficiency-related T-cell lymphomas.

1. *Mimics of malignant T-cell proliferations:* various T-cell proliferations, which are often rich in large transformed cells, are particularly susceptible to overdiagnosis as lymphoma based on their high turnover and large cell appearance.[21] Well-known examples are those associated with phenytoin or with Kikuchi-Fujimoto disease; the issue is also illustrated by a case submitted by Dr Shao, SH2015-465 **Image 2A**, which is a striking example of a florid immunoblastic infiltrate that morphologically mimics an aggressive lymphoma in adult-onset Still disease. Case SH2015-374, submitted by Drs Elliot, Venkatraman, and Catherwood **Image 2B**, is a remarkable example of follicular T-cell hyperplasia with accompanying germinal center B-cell depletion. This case mimics a follicular pattern T-cell lymphoma in a patient with immune thrombocytopenic purpura treated with multiple immunosuppressants combined with targeted anti-CD20 immunotherapy. Case SH2015-334, submitted by Dr Nasr and colleagues, is a clear-cut example of a benign reversible clonal γδ T-cell expansion. The patient had an acute infection with human granulocytic anaplasmosis (formerly known as human granulocytic ehrlichiosis) associated with secondary hemophagocytic lymphohistiocytosis, and the clonal γδ T-cell expansion was reversible with doxycycline treatment. This is not an idiosyncratic finding; γδ T-cell lymphocytosis accounting for 41% to 97% of T cells has been reported in the setting of acute anaplasmosis.[22] A second case of marked benign bone marrow γδ T-cell expansion (SH2015-245, submitted by Dr Nasr) was described in a cardiac transplant recipient who had recently received an influenza vaccination and was rotavirus positive; this patient also had features of hemophagocytic lymphohistiocytosis.
2. *Are atypical hyperplasias precursor lesions to overt malignancy?* For EBV-driven B-cell proliferations in the immunodeficiency setting, a linear evolution from reactive hyperplasias to overt lymphoma is likely. Thus far, there is not sufficient evidence to support a

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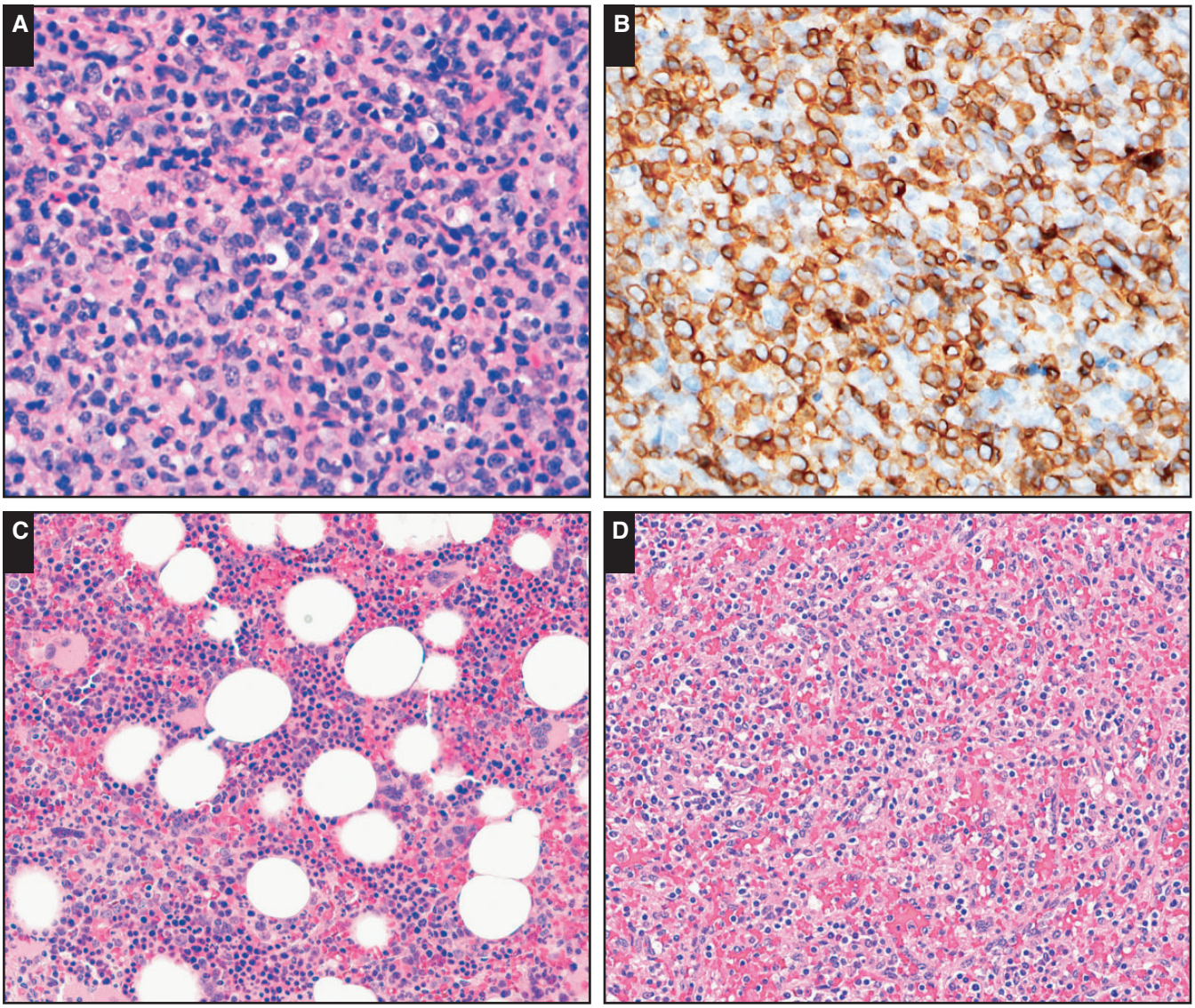

Image 2 Immunodeficiency-related T-cell hyperplasia at nodal and extranodal sites can raise concern for lymphoma. (**A**) SH2015-465: lymphadenopathy in a patient with adult-onset Still disease. The florid immunoblastic infiltrate morphologically mimics an aggressive lymphoma. (**B**) CD3 immunohistochemistry highlights sheets of morphologically malignant-appearing T cells. (**C**) SH2015-503: bone marrow γδ lymphocytosis in a patient with Crohn disease and history of tumor necrosis factor α inhibitor use; the infiltrate is subtle and does not result in architectural distortion. (**D**) SH2015-144 illustrates a reactive γδ T-cell expansion in the splenic red pulp, mimicking hepatosplenic T-cell lymphoma or T-cell large granular lymphocyte leukemia. The infiltrate is monomorphous but cytologically bland and nondestructive, and T-cell gene rearrangement studies are polyclonal. (**A**, H&E, **B**, ×40; **C**, **D**, H&E, ×20)

similar model for all T-cell proliferations. Interesting observations can be made from γδ T-cell proliferations, however. TNFα inhibition, especially in combination with thiopurines, is associated with the development of HSCTL as discussed above but has also been shown to cause expansions of peripheral blood γδ T cells in patients with Crohn disease[23] and psoriasis.[24] These expansions can be clonal but lack all other clinical and histologic features of HSTCL. Case SH2015-503, submitted by Dr Jamali, illustrates the diagnostic dilemma of clonal γδ T-cell lymphocytosis in the bone marrow of a patient with a history of Crohn disease **Image 2C**. The differential diagnosis includes HSTCL[25] and, to a lesser extent, given the clinical setting, the γδ variant of T-cell large granular lymphocytosis.[26] In this case, despite the clonal expansion, there is a lack of the aggressive clinical picture of HSTCL, and a concomitant lack of sinusoidal expansion by atypical lymphoid cells favors a benign clonal expansion that should be monitored closely

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rather than aggressively treated. These proliferations, as well as the T/NK-cell proliferations in primary immune deficiencies discussed in part 5, remain ambiguous in terms of possible increased future risk of overt T-cell lymphoma.

These workshop cases underline the variety and sometimes combination of immune etiologies that can be associated with prominence of particular T-cell subsets. They also emphasize the importance of not overdiagnosing an aggressive T-cell lymphoma such as HSTCL based on relatively nonspecific features such as associated hemophagocytic lymphohistiocytosis or clonality results based on T-cell gene rearrangement studies. T-cell expansions can also involve the spleen, as is nicely illustrated in case SH2015-144, submitted by Dr Zhang **Image 2D**, which occurred in a patient with suspected autoimmune cytopenias. This patient had marked splenomegaly (905 g) with subtle red pulp γδ T-cell infiltrates that failed to demonstrate the isochromosome 7q characteristic of HSCTL. T-cell gene rearrangement studies were polyclonal. To avoid overdiagnosing T-cell lymphoma in cases that may instead represent expansion of functional T-cell subsets, a full clinicopathologic correlation should be sought, including a history of immunodeficiency or immune dysregulation. Morphology remains a starting point, and recognizing architectural distortion is essential. Equally important is awareness of normal tissue distribution of T-cell subsets, such as γδ T cells in spleen and at mucosal sites, together with awareness of expected expansions of those subsets in specific clinical settings, such as a mucosal γδ T-cell lymphocytosis in celiac disease.[27] Apparent phenotypic "abnormalities" should be checked against known immunoprofiles of potentially expanded T-cell subsets, such as the CD5-negative phenotype of the Vδ1 subset of γδ T cells.[28]

Nonclonal T-cell gene rearrangement studies help decrease suspicion for lymphoma, but clonal gene rearrangements are not sufficient to diagnose lymphoma as these may also result from a clonal antigen-driven expansion or, particularly at mucosal sites, from expansion of innate immune T-cell subsets. The latter may exhibit very limited antigen specificity, such as invariant NK/T-cells and mucosal-associated invariant T cells, some of which can show a double-negative (CD4/CD8 double-negative) immunophenotype.[29] In case of uncertainty, it may be best to communicate that uncertainty and recommend close clinical follow-up rather than render a diagnosis that may prompt unnecessary chemotherapy.

Systemic EBV+ T- and NK-Cell LPDs

The most common EBV+ NK-cell or T-cell lymphoma is extranodal NK/T-cell lymphoma, nasal type, and was the first NK-cell or T-cell lymphoma to be clearly linked to EBV. However, our understanding of EBV-driven T-cell and NK-cell proliferations has greatly expanded in recent years. They range in clinical aggressiveness from chronic disorders to fulminant disease with death often in a matter of weeks **Table 2**. Most occur with increased frequency in Asians and in indigenous populations from Central and South America and Mexico. The spectrum of disease is more clearly delineated in the upcoming revision of the WHO classification and somewhat modified from the 2008 monograph.[7]

Table 2
Classification of EBV+ T- and NK-Cell Lymphoproliferative Disorders[a]

EBV-associated hemophagocytic lymphohistiocytosis
Systemic CAEBV
CAEBV, cutaneous
Severe mosquito bite allergy
Hydroa vacciniforme–like T/NK-cell LPD
Systemic EBV+ T-cell lymphoma of childhood
Aggressive NK-cell leukemia
Extranodal NK/T-cell lymphoma, nasal type
Nodal T/NK-cell lymphoma, EBV+[b]

CAEBV, chronic active Epstein-Barr virus infection; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder; NK, natural killer.
[a]Classification adopted by the revised fourth edition World Health Organization[1] classification.
[b]Included within the category of peripheral T-cell lymphoma not otherwise specified.

Many EBV+ T-cell and NK-cell disorders occur preferentially in the pediatric age group and include two major groups: chronic active EBV infection (CAEBV) and systemic EBV+ T-cell lymphoma of childhood.[30,31] CAEBV of T/NK type shows a broad range of clinical manifestations from indolent forms such as hydroa vacciniforme (HV)–like LPD and severe mosquito bite allergy to a more systemic form characterized by fever, hepatosplenomegaly, and lymphadenopathy with or without cutaneous manifestations.[32-35] Systemic EBV+ T-cell lymphoma of childhood—no longer referred to as a "LPD"—has a very fulminant clinical course usually associated with a hemophagocytic syndrome. The differential diagnosis includes acute EBV-associated hemophagocytic lymphohistiocytosis (HLH), which can present acutely, but in some patients responds well to the HLH 2004 protocol[36] and is not considered neoplastic. Nodally based EBV+ peripheral T-cell lymphomas are uncommon and included under the broad heading of PTCL NOS. They are generally monomorphic and lack the angioinvasion and necrosis of extranodal NK/T-cell lymphoma. They most often present in older adults and also can be seen in the posttransplant setting and other immunodeficiency states.[37-39] The cases presented at the workshop included a wide spectrum of these disorders.

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Hemophagocytic Lymphohistiocytosis

EBV can precipitate an acute disorder known as HLH, characterized by a markedly exaggerated immune response to usually acute EBV infection. Patients with HLH present with fever, splenomegaly, and cytopenias. Biopsy specimens may show evidence of hemophagocytic activity, which is usually most evident in bone marrow aspirate smears. The diagnosis of HLH is established with the presence of five of the eight clinical criteria: fever, splenomegaly, cytopenias affecting at least two lineages, elevated triglycerides or hypofibrinogenemia, cytologic evidence of hemophagocytosis, elevated ferritin, and elevated soluble CD25. Patients with EBV-induced HLH usually have a high EBV viral load in blood. NK-cell activity is usually low or absent. HLH can be primary or secondary. Primary HLH is a familial disorder caused by mutations in a variety of genes that lead to impaired cytotoxic function by NK cells or cytotoxic T cells. *PRF1* (perforin) was the first gene to be associated with familial HLH, but the number of genes associated with the syndrome has expanded in recent years.[40]

EBV-associated HLH in the absence of predisposing genetic aberrations usually presents in young children. It is more common in Asians, with many reports coming from Taiwan, Japan, and Korea. In the Western hemisphere, it is more commonly seen in indigenous populations from Mexico, Central America, and South America. Genetic factors clearly play a role, but the precise genes that predispose to the syndrome have not been identified. The median age at onset is approximately 4 years, with many cases presenting in children younger than 3 years. This is an acute illness that requires immediate therapeutic intervention. The HLH 2004 protocol includes etoposide, dexamethasone, and cyclosporine A, which may be effective in many cases. Remissions are accompanied by a reduction in the EBV viral load, particularly reduced viral load in T/NK-cell fractions, as opposed to the B-cell fraction. The differential diagnosis of EBV-associated HLH includes CAEBV of T-cell or NK-cell type or systemic EBV+ T-cell lymphoma of childhood. The latter conditions require more aggressive therapeutic intervention, with allogeneic stem cell transplantation. In EBV-associated HLH, clonality may be found in the T-cell receptor (TCR) genes, so evidence of a monoclonal process does not necessarily indicate an underlying T-cell lymphoma.

Case SH2015-135, submitted to the workshop by Drs Gaurav Gupta and Monika Pilichowska of Tufts University, was an example of acute EBV-associated HLH in a 3-year-old Asian female. She had no significant medical and/or family history. She presented with fever, septic shock, multiorgan failure, and pancytopenia (WBC, 2.7 $\times$ 10^3/μL; RBC, 2.9 M/μL; hemoglobin, 7.7 g/dL; hematocrit, 22.1; platelets, 24 $\times$ 10^3/μL). Laboratory studies showed a markedly elevated ferritin level of more than 40,000 ng/mL, lactate dehydrogenase level of 5,744 IU/L, and markedly elevated triglycerides of 324 mg/dL. Bone marrow examination showed marked hemophagocytic activity and diffuse interstitial infiltration by EBV+ T cells **Image 3**. Polymerase chain reaction (PCR) studies for T-cell receptor γ (TCRG) gene rearrangement showed an oligoclonal pattern. EBV DNA in whole blood was markedly elevated. A genetic screen for primary HLH by next-generation sequencing performed at Children's Hospital in Cincinnati, Ohio, was negative. Therapy was initiated with the HLH 94 protocol, with the addition of bortezomib. She responded with decline in inflammatory markers and reduction in the EBV viral load. Moreover, with treatment, EBV was cleared from the T/NK-cell fraction, with persistent low levels in B cells. At 1 year following treatment, the patient was well with normal EBV levels consistent with chronic carrier state. Two similar cases were submitted for the workshop, one in a 2-year-old Vietnamese boy (SH2015-143) and one in a 2-year-old Mexican boy (SH2015-15). Both children recovered following treatment for HLH.

Another case of HLH (SH2015-462) associated with EBV presented in a 59-year-old man who had undergone therapy for EBV+ extranodal NK/T-cell lymphoma. The patient was felt to be in complete remission but developed EBV-associated viremia and an HLH picture. EBV+ T cells were identified in the bone marrow and a clonal TCRG rearrangement was identified, which was distinct from the NK-cell phenotype of the prior lymphoma. The absence of cytologic atypia in the EBV+ T cells argued against a diagnosis of EBV+ T-cell lymphoma. The clinical picture resembled that of CAEBV, but CAEBV is rare in adult life and is usually diagnosed in children, following recent EBV infection.

Case SH2015-433, submitted by Dr Sohail Qayyum from Children's Hospital in Philadelphia, was an example of primary HLH associated with mutations in perforin. The patient was an 18-year-old man who presented acutely with an HLH-like picture with hepatic dysfunction, coagulopathy, anemia, and thrombocytopenia. A lymph node biopsy specimen showed diffuse infiltration by EBV+ cells, with increased EBV+ cells also seen in the bone marrow. Marked hemophagocytic activity was seen in the bone marrow. While double staining was not performed, the number and atypia of the B cells in the lymph node suggested that EBV was primarily localized to B cells and not T cells. The patient was heterozygous for two mutations affecting *PRF1:* alle1e 2: c. 1122G > A (p. W374*) and allele 1: c.272C > T (p . A91V). The patient was treated with high-dose steroids and antithymocyte globulin, in addition to blood product support and

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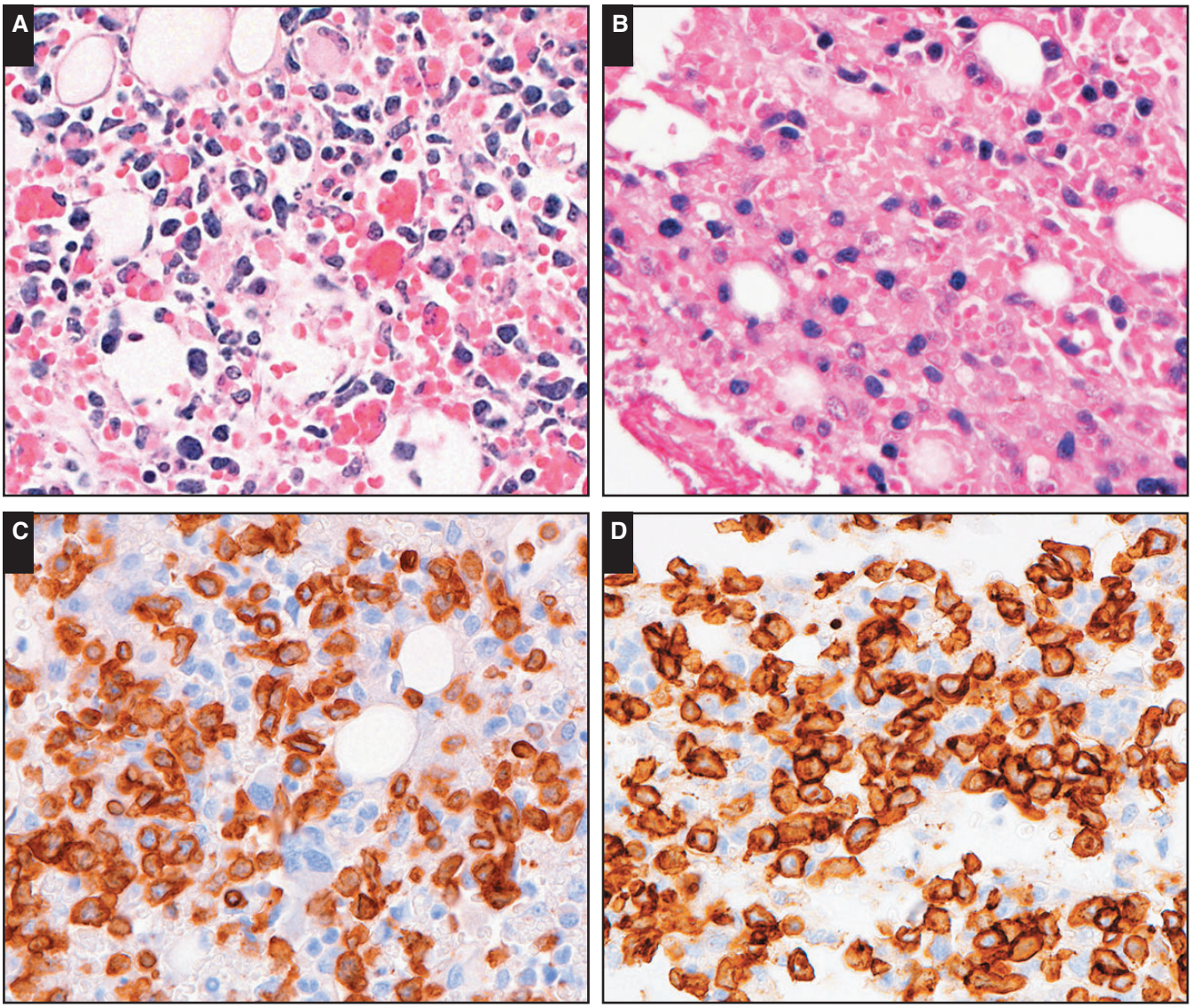

Image 3 Epstein-Barr virus (EBV)–associated hemophagocytic lymphohistiocytosis (HLH). (**A**) The bone marrow contains an interstitial infiltrate of lymphocytes, some showing cytologic atypia. Background histiocytes show marked erythrophagocytosis. (**B**) Infiltrating lymphoid cells are positive for EBV-encoded small RNA and also positive for CD3 (**C**) and CD8 (**D**). Polymerase chain reaction studies for T-cell receptor γ showed a polyclonal pattern, and the patient responded to therapy for HLH (case SH2015-135). (**A**, **B**, H&E; **A**-**D**, ×40)

antibiotics. The patient died 2.5 weeks following admission. In a survey of 500 Italian patients with HLH, biallelic pathogenic mutations were found in 34% of patients, the proportion being much higher (64%) in patients diagnosed in the first year of life. Of 281 patients defined as having sporadic HLH, without a family history, 15% had monoallelic mutations in one of the genes defining familial HLH.[41]

Several additional cases of primary or secondary confirmed HLH or probable HLH were presented at the workshop, reflecting the various clinical settings in which HLH may be diagnosed. Two were associated with infection, histoplasmosis in one case (SH2015-367) and probable rotavirus infection in a second case (SH2015-246). A third case (SH2015-87) was diagnosed in a 7-year-old boy with T-cell acute lymphoblastic leukemia. One case (SH2015-334) in a patient with anaplasmosis exhibited hemophagocytosis in the bone marrow but otherwise did not meet clinical criteria for HLH. Two additional cases were idiopathic.

Chronic Active EBV Infection

CAEBV has been defined as a systemic EBV+ LPD characterized by fever, lymphadenopathy, and splenomegaly developing after primary virus infection in patients

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Table 3
Diagnostic Features of Systemic Chronic Active EBV Infection of T/NK-Cell Type

Feature	Description
Definition	CAEBV-T/NK is a systemic EBV+ polyclonal, oligoclonal, or often monoclonal T- or NK-cell lymphoproliferative disorder
Diagnostic criteria	High viral load in peripheral blood or tissues
	Intermittent or persistent infectious mononucleosis-like symptoms such as fever, lymphadenopathy, and hepatosplenomegaly for at least 3 months
	No known immunodeficiency
Clinical features and behavior	Prevalent in Asia and Latin America
	Most patients are children or young adults
	Often accompanied by hydroa vacciniforme or mosquito bite hypersensitivity
	High antibody titers against EBV VCA IgG and early antigen IgG
	Poor prognostic factors: late onset of disease, thrombocytopenia, EBV infection in T cells
	Cause of death: hemophagocytic syndrome, multiple-organ failure, T- or NK-cell malignancy
Morphology	Variable with paracortical hyperplasia
	Polymorphic infiltrates of inflammatory cells with granuloma and focal necrosis
	No significant atypia in infiltrating cells
	Sinusoidal infiltration by small lymphocytes without atypia in liver

CAEBV, chronic active Epstein-Barr virus infection; EBV, Epstein-Barr virus; IgG, immunoglobulin G; NK, natural killer; VCA, viral capsid antigen.

without known immunodeficiency.[42] Affected patients have high levels of EBV DNA in the blood, histologic evidence of organ disease, and elevated levels of EBV RNA or viral proteins in affected tissues. While initially proposed as a progressive EBV infection of B cells as the primary target, the term as used in the recent literature refers to an aggressive EBV+ T-cell, NK-cell, or B-cell LPD, mainly affecting persons of Asian origin.[43] The initial criteria proposed a requirement of 6 months for persistence of symptoms after primary EBV infection, but more recently modified criteria of 3 months for duration of symptoms have been suggested.[31] EBV serology reveals, in most patients, high antibody titers against EBV viral capsid antigen (VCA) immunoglobulin (IgG) and early antigen IgG. EBV immunoglobulin M VCA titers decrease in most patients after 3 to 6 months and are often negative at the time the diagnosis is made. All patients have increased levels of EBV DNA ($>10^{2.5}$ copies/mg EBV DNA) in peripheral blood. Most cases of CAEBV have been reported from Japan,[5] but other reports have come from series in Korea[44] and Taiwan.[45] Fewer reported cases have been seen in both white and indigenous populations in the Americas, mainly from Central and South America,[45] and rare cases from Africa.[46]

Markedly elevated levels of EBV DNA are found in the peripheral blood, and increased cells infected by EBV are detected in tissues using EBV-encoded small RNA (EBER) in situ hybridization. Three different disorders are included under the heading of CAEBV of T-cell or NK-cell type: systemic CAEBV and the two cutaneous forms of CAEBV: HV-like LPD and severe mosquito bite allergy **Table 3**. However, some patients with cutaneous disease have systemic symptoms, and progression to systemic CAEBV or EBV+ T-cell or NK-cell lymphoma can occur.[47] Patients with systemic disease present with fever, hepatic dysfunction, splenomegaly, lymphadenopathy, and thrombocytopenia. Systemic CAEBV can be polyclonal, oligoclonal, or monoclonal, and in one proposal from the CAEBV study group, clonality has been used as a major factor in subclassification and prediction of prognosis.[32] Cases with monoclonality present a challenging differential diagnosis with systemic EBV+ T-cell lymphoma, and the presence of cytological atypia in the setting of a monoclonal TCR gene rearrangement favors systemic EBV+ T-cell lymphoma of childhood.

In systemic CAEBV, the EBV-infected cells, T cells, or, less commonly, NK cells diffusely infiltrate many organs, including bone marrow, liver, lymph nodes, and spleen. However, a variety of sites can be involved, including the gastrointestinal tract, as seen in one case presented at the workshop (SH2015-151) by Dr Siok Bian Ng from Singapore. This case was unusual in that the patient, a 15-year-old Asian girl, had a history of a polymorphic B-cell posttransplant lymphoproliferative disorder (PTLD) involving the tonsils presenting 6 months following a renal transplant for chronic glomerulonephritis. The patient was treated with rituximab, and immunosuppression was reduced. Five years after the initial renal transplant, the patient developed hemophagocytosis, treated with the 2004 HLH protocol. Cytopenias persisted and the patient exhibited hematochezia, with endoscopy showing multiple mucosal ulcers in the terminal ileum. The patient was treated with a limited right hemicolectomy. The final diagnosis from the contributor and panel was CAEBV of T-cell type. In CAEBV, the density of the EBER+ cells is usually not great, and the architecture of affected tissues is preserved **Image 4**. However, a hemophagocytic syndrome

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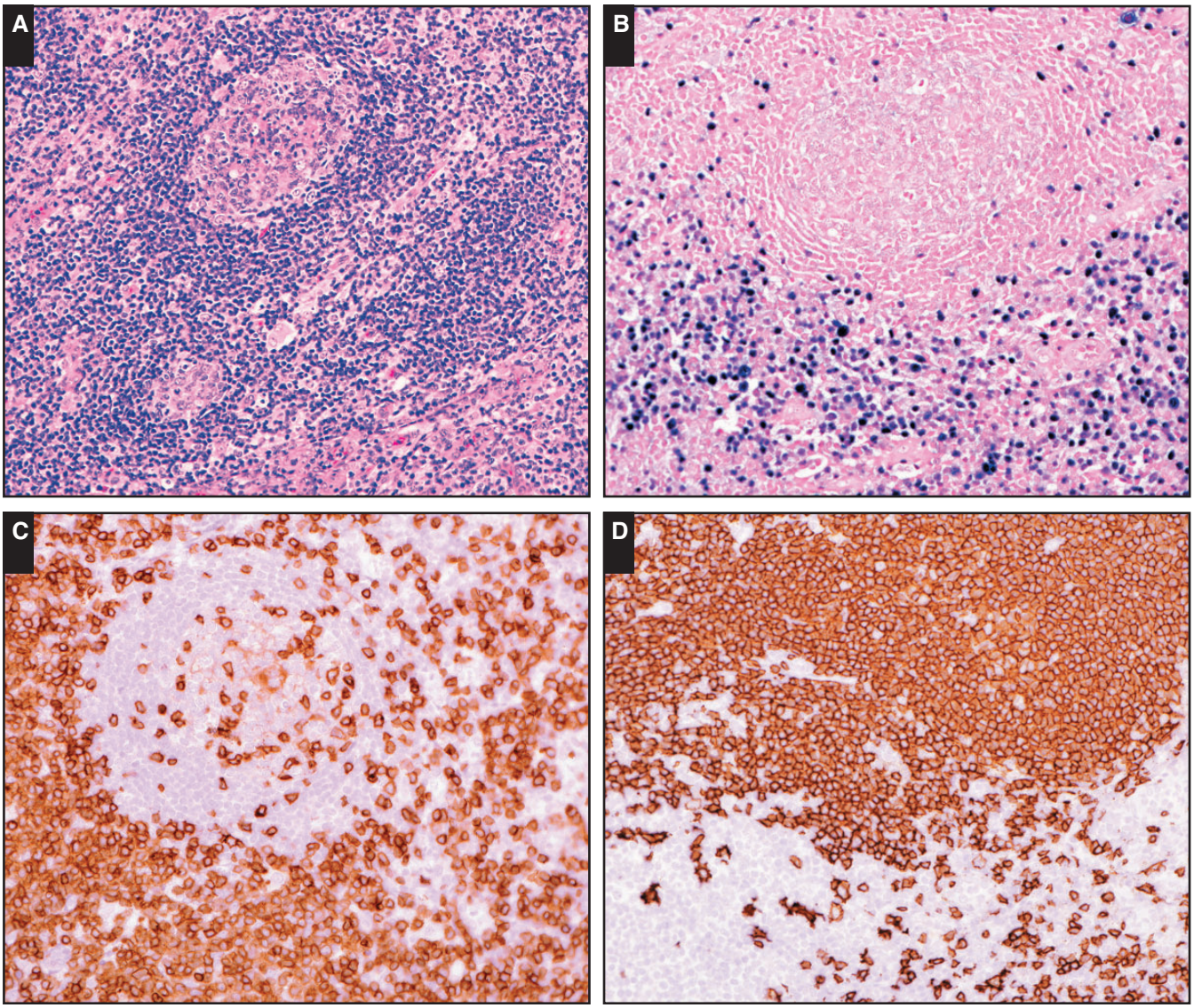

Image 4 Chronic active Epstein-Barr virus (EBV) infection of T-cell type, involving the appendix. This 9-year-old girl had acute infectious mononucleosis. Symptoms persisted for more than 10 months. She had persistent fevers, hepatosplenomegaly, and pan-colitis, affecting the gastrointestinal tract. (**A**) Section of the appendix shows lymphoid hyperplasia, with reactive lymphoid follicles. (**B**) An EBV-encoded small RNA (EBER) stain shows numerous EBV-positive cells in the perifollicular region. (**C**) CD3 stains the interfollicular cells, corresponding to the distribution of EBER positivity, while CD20 (**D**) stains the reactive follicles. T cells were polyclonal by T-cell receptor γ polymerase chain reaction. (**A**, **B**, H&E, ×10; **C**, **D**, ×20)

may develop, which may alter the histologic picture due to expansion of activated histiocytes. The EBER-positive cells generally do not show cytologic atypia.

Hydroa Vacciniforme

HV was originally described as a benign photodermatosis in which exposure to sunlight results in vesicles that ulcerate and evolve to crusts and scars after healing.[48] Subsequent studies in Asian populations showed that HV was an EBV-associated disorder.[49] EBV+ T cells and, less often, NK cells infiltrate the superficial dermis. In severe cases, the infiltrate is more extensive and the clinical manifestations more severe, with marked facial edema, vesicles, crusts, and cutaneous ulcers. In advanced cases, the lesions are not limited to sun-exposed areas, and in the 2008 WHO classification, these severe forms were referred to as HV-like lymphoma.[50] However, due to the broad spectrum of the disease and the difficulty in drawing a sharp distinction between some cases of HV and HV-like lymphoma, the revised WHO classification has chosen the term *HV-like LPD*

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to encompass the clinical spectrum.[7] The EBV-infected T cells vary in their phenotype. Most cases are CD8+, but some are CD4+, and some have an NK-cell phenotype with expression of CD56. There remains a small group of cases of classic HV that has a low risk of progression and usually resolves spontaneously as patients reach adult life. It is not clear whether all such cases are associated with EBV.[51]

Severe Mosquito Bite Allergy

Severe mosquito bite allergy is characterized by intense local skin lesions, including ulcers and bullae.[52] Patients have circulating EBV+ NK cells in the peripheral blood and are at risk for HLH. Most of the cases have been reported in Asians and more rarely in Hispanics. The condition affects children, and as with HV-like LPD, the condition may remit spontaneously in adulthood or progress to a more aggressive EBV+ lymphoma or aggressive NK-cell leukemia.

Seven cases submitted to the workshop were diagnosed as CAEBV. The patients ranged in age from 7 to 50 years, with a median age of 18 years and an equal male-to-female ratio. Two patients were Asian, two were Hispanic, one was white, and the ethnic background was not specified in two cases. Two of the cases arose in a setting of underlying immunodeficiency, while most of the cases were sporadic. Case SH2015-151 was submitted by Siok-bian Ng from the National University of Singapore. A 15-year-old Asian girl had a renal transplant for chronic glomerulonephritis. Ten months after transplant, she was diagnosed with polymorphic PTLD of B-cell type involving the tonsil. She was treated with rituximab, with reduction of immunosuppression. Her symptoms resolved with resolution of fludeoxyglucose positron emission tomography avid lesions; however, EBV viral load remained high. Approximately 4.5 years after transplant, she developed acute cellular rejection of the kidney, followed by HLH and pancytopenia. A bone marrow biopsy specimen showed an EBV+ T-cell infiltrate in the marrow. She was treated successfully with the HLH 2004 protocol but several months later developed multiple ileal ulcers with involvement by a polymorphic EBV+ T-cell infiltrate that was monoclonal by TCRG PCR. Nephrectomy was performed for graft failure, and over the ensuing 2 years, her EBV DNA titers remained high. A colon biopsy specimen showed involvement a polymorphic T-cell infiltrate. Eight years after transplant, the patient has remained alive with disease without aggressive treatment. The differential diagnosis in this case was between CAEBV of T-cell type and systemic EBV+ T-cell lymphoma. Overall, the presenter and panel favored a diagnosis of CAEBV based on the chronic and protracted clinical course with limited treatment and the polymorphic nature of the infiltrate, despite the presence of a clonal T-cell process. Using the classification proposed by the CAEBV study group, a diagnosis of A2 subtype of CAEBV was considered.[32]

A second case of CAEBV arising in a setting of immune suppression (SH2015-249) was submitted by Drs Sergei Syrbu, Deqin Ma, and Nancy Rosenthal from the University of Iowa. The patient was a 15-year-old girl with a 2-year history of juvenile rheumatoid arthritis treated with a TNF inhibitor (etanercept). She also had a 7-year history of palmoplantar dermatitis diagnosed on a biopsy specimen as an EBV+ process resembling mosquito bite hypersensitivity. The patient was noted to have had mild cytopenias and elevated liver enzymes, suggestive of CAEBV. She had an elevated EBV DNA viral load, and etanercept therapy was discontinued. Her symptoms persisted with cervical and inguinal lymphadenopathy and persistent fever. Lymph node biopsy specimen showed a polymorphic T-cell infiltrate with scattered large atypical cells. The infiltrate was diffusely positive for CD3, CD2, CD8, and EBER, with negative B-cell markers. TCRG PCR showed multiple (four) peaks in the lymph node, but two dominant peaks were seen in both the blood and lymph node, suggesting the presence of a systemic clonal process. The panel diagnosis was CAEBV of T-cell type with progression to systemic EBV+ T-cell lymphoma. It is not clear what role the immunosuppressive therapy played in her illness since her symptoms of CAEBV in the skin antedated immunosuppressive treatment for several years.

Two additional cases of cutaneous CAEBV were submitted, one in a 7-year-old Hispanic girl (SH2015-311) and a second in an 18-year-old white man (SH2015-235). Both were of NK-cell type and had features of mosquito bite hypersensitivity. Long-term follow-up was not available in the first case. The second case had a 4-year history, eventually progressing to aggressive NK-cell leukemia. There were three cases best categorized as systemic forms of CAEBV of T-cell type presenting in a 16-year-old Hispanic girl (SH2015-152), a 50-year-old Asian man (SH2015-466), and a 25-year-old man (SH2015-202). Two of the patients progressed to an aggressive T-cell lymphoma within 4 years. Case SH2015-202 was unusual in that the patient developed myocarditis, leading to heart failure and need for cardiac transplantation.

Conclusions

Table 4 provides a succinct overview of key themes from the workshop session on T- and NK-cell LPDs in the immunodeficiency setting. Briefly, awareness of lymphoma mimics in the form of expansion of normal T-cell subsets is paramount. The clinical context, particularly underlying rheumatologic, autoimmune, infectious, iatrogenic, or other immune deficiency or dysregulatory conditions, is particularly important. A small subset of WHO-defined T/NK

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Table 4
Summary Table: T- and NK-Cell Lymphomas Associated With Immunodeficiency/Immune Stimulation

Hyperplasias of T-cell subsets can mimic lymphoma.
γδ T-cell expansions, sometimes clonal, can be seen in the setting of infection and iatrogenic immunosuppression.
Large cell/immunoblastic proliferations, some with associated necrosis, can be seen in the rheumatologic, autoimmune, or infectious settings.
Follicular helper T-cell hyperplasia can be particularly prominent when B cells are iatrogenically depleted.
Clonal gene rearrangements are not sufficient to diagnose lymphoma.
Clonal antigen-driven expansion may reverse upon treatment of infection.
Innate immune T-cell subsets with very limited antigen specificity may produce spuriously clonal results.
Spectrum of T and NK lymphomas in immunodeficiency is similar to nonimmunodeficiency settings.
Among cases submitted to the workshop, most WHO entities are represented, and most peripheral T-cell lymphomas are EBV–.
Most T-cell lymphomas may be coincidental to the immunodeficiency state.
Causal relationship is plausible in subset of cases, such as EBV+ primary cutaneous anaplastic large cell lymphoma in the HIV setting, or presentation in an unusual population such as angioimmunoblastic T-cell lymphoma in a child posttransplant.
A subset of T-cell lymphomas is etiologically linked to specific immunodeficiency and/or chronic immune stimulation.
Hepatosplenic T-cell lymphoma is linked to iatrogenic immunosuppression, particularly thiopurines and/or TNFα inhibitor in Crohn disease/ulcerative colitis.
A WHO-recognized indolent variant of anaplastic large cell lymphoma is associated with breast implants.
Follicular helper T-cell–derived lymphomas, such as angioimmunoblastic T-cell lymphoma and follicular T-cell lymphoma, can be associated with immune dysfunction.
Follicular helper T-cell–derived lymphomas often harbor secondary B-cell proliferations, which can mimic immunodeficiency-related B-cell proliferations.
The secondary B-cell proliferations can resemble Hodgkin lymphoma, large B-cell lymphoma, or polymorphic B lymphoproliferative disorder, EBV+ or EBV–.

EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; NK, natural killer; TNFα, tumor necrosis factor α; WHO, World Health Organization.

Table 5
Summary Table: Systemic EBV+ T- and NK-Cell Lymphoproliferative Disorders

EBV+ hemophagocytic lymphohistiocytosis is a nonneoplastic proliferation mainly seen in young children, most often of Asian origin.
It presents acutely, without an antecedent history of immunodeficiency or prior EBV infection.
The initial treatment approach employs the HLH 2004 protocol.
T-cell monoclonality can be seen in approximately 60% of cases and does not necessarily indicate a neoplastic process.
Poor prognostic factors include hyperbilirubinemia (>1.8 mg/dL) and hyperferritinemia (>20,300 ng/mL) at the time of diagnosis.
Lack of response to the HLH 2004 protocol may indicate the need for allogeneic bone marrow transplantation.
Precipitating causes, other than EBV, include infection and malignancy.
Chronic active EBV infection (CAEBV) (T/NK) is associated with immunodeficiency in a subset of patients with good response to steroids.
CAEBV includes both systemic and cutaneous presentations, but patients with cutaneous disease may have systemic symptoms.
CAEBV may follow a chronic, relapsing clinical course, with a risk of progression to systemic EBV+ T-cell lymphoma.
CAEBV, when it arises de novo or in the setting of immunodeficiency, is more common in certain ethnic or racial groups (Asian, Hispanic).
CAEBV in the setting of immunodeficiency has an older age at onset than sporadic cases, which are nearly always in children or adolescents.
Mosquito bite hypersensitivity is usually of NK-cell origin, while hydroa vacciniforme is usually of T-cell derivation.
Systemic EBV+ T-cell lymphoma is rarely associated with various immunodeficiency settings and is an acute, de novo lymphoma with a fulminant clinical course.
Diverse ethnic origins are seen, but most patients are Asian or Hispanic.
Most cases are accompanied by a hemophagocytic syndrome.
A spectrum of cytologic atypia can be seen, with some cases containing markedly pleomorphic cells.
Systemic EBV+ T-cell lymphoma in the setting of immunodeficiency has an older age at onset than sporadic cases.
Setting: These lesions most often present in immunocompetent patients.
Epidemiologic data suggest genetic risk.

CAEBV, chronic active Epstein-Barr virus infection; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; NK, natural killer.

lymphomas is definitely or plausibly associated with underlying immunodeficiency or immune dysregulation states, but the bulk of mature T-cell lymphomas occurring in this setting may in fact be coincidental. Given that immune deficiency and T-cell lymphomas of the follicular helper cell phenotype may both predispose to B-cell proliferations, often EBV+ and often polymorphous and/or containing Hodgkin-like cells, both an underlying T-cell lymphoma and an underlying immune deficiency should be considered in the differential diagnosis when these findings predominate.

The broad clinical and pathologic spectrum of systemic EBV+ T-cell and NK-cell LPDs is summarized in **Table 5** and demonstrated in **Image 5**. Most cases arise sporadically,

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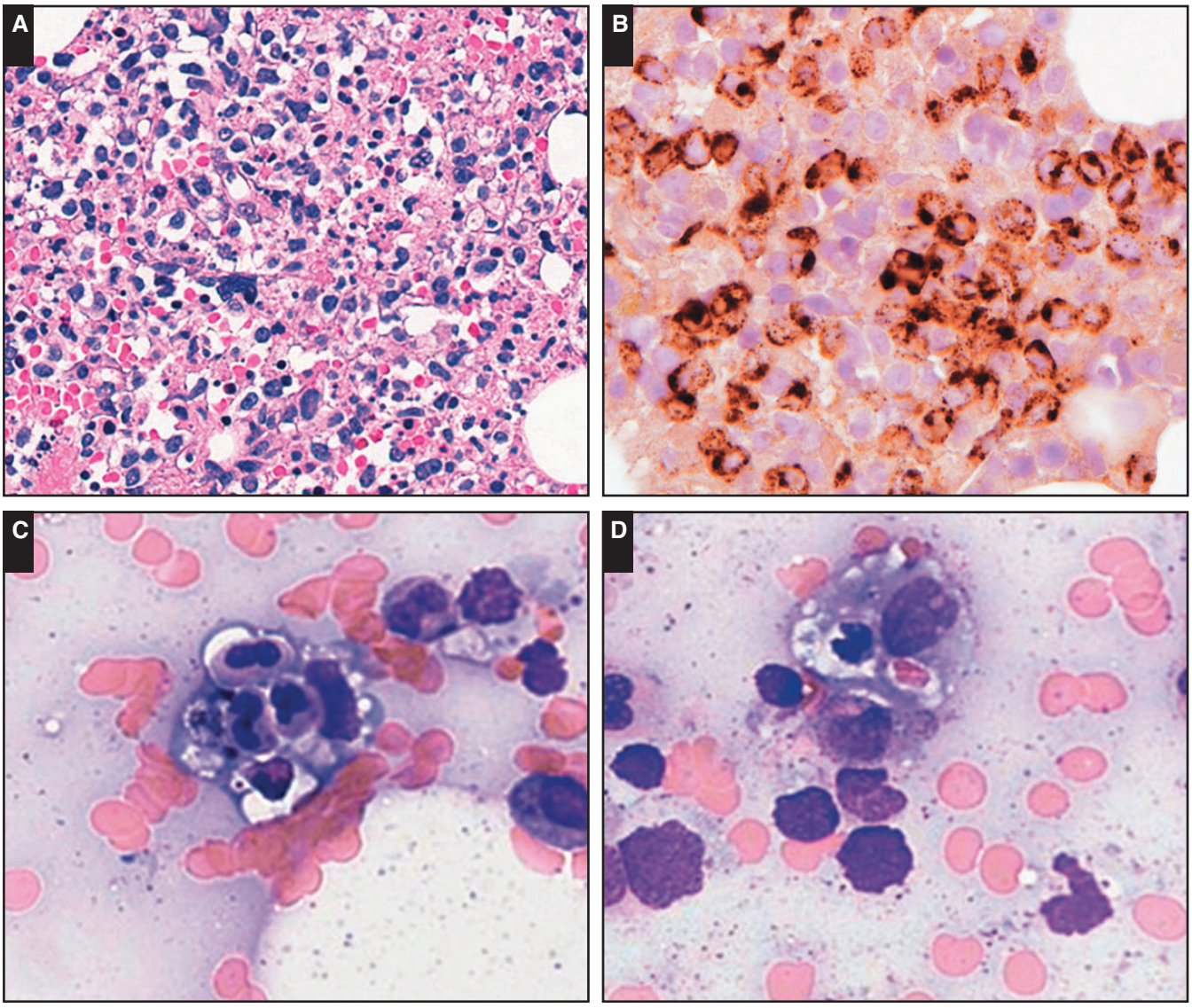

Image 5 Systemic Epstein-Barr virus (EBV)–positive T-cell lymphoma, posttransplant. This 57-year-old man developed an aggressive T-cell lymphoma involving the bone marrow 14 years after a cadaveric renal transplant. His presentation was complicated by hemophagocytic lymphohistiocytosis. (**A**) Bone marrow core biopsy specimen is diffusely infiltrated by atypical lymphoid cells. (**B**) Lymphoid cells are positive for CD3 and were clonal by T-cell receptor γ polymerase chain reaction. (**C**, **D**) Marked hemophagocytic activity in the bone marrow smear (case SH2015-193). (**A**, H&E, **B**, ×40; **C**, **D**, Giemsa, ×100)

without a history of congenital or iatrogenic immunodeficiency. However, both CAEBV and systemic EBV+ T-cell lymphoma were sometimes observed in the setting of immunodeficiency, usually iatrogenic. Such cases arise at an older age at onset and do not show the strong genetic predisposition of cases of sporadic disease. The clinical course is comparable for both CAEBV and systemic EBV+ T-cell lymphoma.

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To view full-slide images and case write-ups for selected 2015 SH/EAHP Workshop case numbers mentioned in this article, go to http://bit.ly/2lT2LTY. If you are not already signed in as an ASCP member you will be first asked to sign in (or create an ASCP account and sign in).

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