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EBV-Positive B-Cell Proliferations of Varied Malignant Potential

2015 SH/EAHP Workshop Report—Part 1

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ABSTRACT

Objectives: *The 2015 Workshop of the Society for Hematopathology/European Association for Haematopathology aimed to review B-cell proliferations of varied malignant potential associated with immunodeficiency.*

Methods: *The Workshop Panel reviewed all cases of B-cell hyperplasias, polymorphic B-lymphoproliferative disorders, Epstein-Barr virus (EBV)–positive mucocutaneous ulcer, and large B-cell proliferations associated with chronic inflammation and rendered consensus diagnoses. Disease definitions, boundaries with more aggressive B-cell proliferations, and association with EBV were explored.*

Results: *B-cell proliferations of varied malignant potential occurred in all immunodeficiency backgrounds. Presentation early in the course of immunodeficiency and in younger age groups and regression with reduction of immunosuppression were characteristic features. EBV positivity was essential for diagnosis in some hyperplasias where other specific defining features were absent.*

Conclusions: *This spectrum of B-cell proliferations show similarities across immunodeficiency backgrounds. Localized forms of immunodeficiency disorders arise in immunocompetent patients most likely due to chronic immune stimulation and, despite aggressive histologic features, often show indolent clinical behavior.*

Upon completion of this activity you will be able to:
- describe the features of nondestructive lesions occurring in immunodeficiency settings.
- discuss the salient histologic, immunophenotypic, and molecular features of polymorphic B-lymphoproliferative disorders.
- define the clinicopathologic features of mucocutaneous ulcers.

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Drs Yasodha Natkunam and John Goodlad chaired Session 1 of the workshop on EBV-positive B-cell proliferations of varied malignant potential and functioned as the co-lead authors of this manuscript. Immunodeficiency-associated B-cell proliferations of varied malignant potential are a heterogeneous group of lesions that represent early manifestations and localized forms of immunodeficiency disorders. They share in common the lack of diagnostic features to be classified as lymphomas as defined in the World Health Organization (WHO) classification for immunocompetent patients.[1,2] Among the early manifestations of immunodeficiency disorders are hyperplasias and polymorphic

lymphoproliferative disorders (polymorphic LPDs), the majority of which are B-cell proliferations driven by Epstein-Barr virus (EBV) that typically lack additional genetic alterations. Hyperplasias in the immunodeficiency setting form nondestructive masses, whereas polymorphic lymphoproliferative disorders cause destructive lesions that may mimic large B-cell or classical Hodgkin lymphomas (CHLs).

Two other entities included in the group of EBV-positive B-cell proliferations of variable malignant potential represent localized forms of immunodeficiency disorders—namely, mucocutaneous ulcer and large B-cell proliferations associated with chronic inflammation. Both lesions are EBV positive, present as well-circumscribed masses or proliferations within confined spaces, and typically occur in immunocompetent patients. Some parallels can be recognized between large B-cell proliferations associated with chronic inflammation and breast implant–associated anaplastic large cell lymphoma. Although they are thought to result from localized loss of host immune surveillance or chronic immune stimulation, their pathogenesis is poorly understood.

The 2015 Society for Hematopathology/European Association for Haematopathology Workshop on Immunodeficiency and Dysregulation received a total of 101 case submissions that were grouped into the following four categories to facilitate review by the expert panel members: (1) B-cell hyperplasias, (2) polymorphic B-lymphoproliferative disorders, (3) mucocutaneous ulcer, and (4) large B-cell proliferations associated with chronic inflammation. Similar lesions occurring in various immunodeficiency backgrounds were evaluated together to allow exploration of unifying themes and disease definitions.

Hyperplasias (Early or Nondestructive Lesions)

Hyperplasias in the immunodeficiency setting are mass-forming lesions characterized by preservation of the involved tissue architecture and lack of distinguishing features of lymphoma. In the posttransplant setting, they usually present at an earlier age than other types of immunodeficiency-associated LPDs and typically occur in children who are seronegative for EBV at the time of transplantation. Hyperplasias much more frequently involve lymph nodes, tonsils, and adenoids than other extranodal sites. They tend to regress spontaneously or with reduction of immunosuppression; rare exceptions with concurrent or subsequent development of aggressive lymphomas or a fatal clinical course have also been reported.[1] Since histologic features of hyperplasias in immunodeficiency settings are often nonspecific and indistinguishable from hyperplasias in immunocompetent hosts, other causes, including infectious and inflammatory etiologies, must be carefully excluded.

In the WHO 2008 classification, the term *early lesions* was used to refer to hyperplasias arising from B cells, but due to the ambiguity of the term *early*, they have been renamed *nondestructive lesions* in the WHO 2016 update.[1,2] In the WHO framework, nondestructive lesions are classified as a posttransplant lymphoproliferative disorder (PTLD). Guidelines for what terminology should be used in diagnostic settings other than solid organ or stem cell transplantation, however, have not been well established. In the interest of exploring common themes in the context of the workshop, we adopted the term *hyperplasias* to allow inclusion of similar lesions in all types of immunodeficiency-related settings. Three subtypes of nondestructive hyperplasias have been formally recognized in the WHO 2016 classification: follicular hyperplasia (FH), infectious mononucleosis-like hyperplasia (IMH), and plasmacytic hyperplasia (PH). IMH and PH in the posttransplant setting were already incorporated in earlier iterations of the WHO classification.

A total of 25 cases of B-cell hyperplasias were submitted to the workshop, with the majority (n = 16) arising in the posttransplant setting. The remaining cases were associated with autoimmune/iatrogenic conditions (n = 8) or with probable immune senescence related to aging (n = 2). A summary of the types of hyperplasia associated with immunodeficiency that were submitted to the workshop is shown in **Table 1**. Hyperplasias due to T-cell proliferations are not included in the WHO classification. The T-cell hyperplasias submitted to the workshop occurred primarily in the iatrogenic/autoimmune setting (n = 3) or primary immunodeficiency setting (n = 3) and are discussed in Session 4; an unusual hematogone hyperplasia associated with congenital phosphatidylinositol 3-kinase Cδ activating kinase mutation is discussed in Session 5 of this report.

Follicular Hyperplasia

Hypertrophy of adenoids and tonsils following solid organ transplantation in children has long been recognized, together with the accompanying histologic findings of FH, usually presenting as florid follicular hyperplasia (FFH).[3-6] Initial studies found no significant differences in histologic features, distribution of EBV, or B-cell clonality in adenotonsillar hypertrophy between PTLD and immunocompetent patients; an increased risk of developing more aggressive PTLD within a 5-year period was also not significantly increased.[3,7] Later studies, however, have suggested that FH may represent a precursor lesion to PTLD.[5,6] Similar to monomorphic and polymorphic PTLD,[8-12] several studies have raised the possibility of including FH as an immunodeficiency-related LPD; however, the lack of

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Table 1
Clinicopathologic Features of B-Cell Hyperplasias Submitted to the Workshop

Case No.	Age, y/Sex	IS	Site	EBER	PCR	Cyto/FISH	Treatment	Outcome
Follicular hyperplasia								
SH2015-123	12/M	PT	Bilateral tonsils	+	BCR+	+	Tonsillectomy	ANED
SH2015-145	5/M	PT	Cervical LN, gastric	+	ND	ND	CHL treated	ANED
SH2015-268	5/F	PT	Tonsils, adenoid	+	ND	ND	Tonsillectomy	ANED
SH2015-357	9/M	PT	Adenoid	+	ND	ND	Adenoidectomy	ANED
SH2015-389	48/F	PT	Cervical LN	+	ND	ND	None	ANED
SH2015-391	23/F	PT	Multiple LN sites	+	ND	ND	None	ANED
SH2015-416	5/F	PT	Bilateral tonsils	+	ND	ND	Tonsillectomy	ANED
SH2015-419	4/F	PT	Cervical LN	+	BCR–	–	None	ANED
SH2015-282	65/M	None	Multiple LN sites	+	BCR–TCR–	46XY	None	ANED
SH2015-214	71/F	None	Cervical LN	+	ND	ND	None	ANED
SH2015-219	54/M	A/I	Axillary LN	+	ND	ND	RIS	ANED
SH2015-330	60/M	A/I	Parotid, axillary LN	–	BCR+	ND	RIS	ANED
SH2015-257	45/M	A/I	Axillary LN	+	BCR– TCR–	ND	None	ANED
SH2015-388	32/F	A/I	Multiple LN site	–	ND	ND	None	ANED
Infectious mononucleosis-like hyperplasia								
SH2015-134	61/F	PT	Axillary LN	+	BCR–	ND	R-prednisone	ANED
SH2015-34	20/F	PT	Bilateral tonsils	+	ND	ND	Tonsillectomy	ANED
SH2015-158	11/F	PT	Inguinal LN	+	BCR+	ND	Tacrolimus	ANED
SH2015-310	30/M	PT	Bilateral tonsils	+	BCR–	ND	Tonsillectomy, R	ANED
SH2015-514	2/M	PT	Tonsils, adenoids	+	ND	ND	Tonsillectomy	ANED
SH2015-77	43/F	A/I	Multiple LN sites	+	BCR+TCR–	ND	Unknown	Unknown
SH2015-163	20/M	A/I	Multiple LN sites	+	BCR–TCR–	ND	Unknown	Unknown
SH2015-329	3/F	A/I	Adenoids, lungs, CNS	+	ND	ND	Unknown	ANED
SH2015-456	34/F	A/I	Inguinal LN, HLH	–	BCR–TCR–	ND	None	DOD
Plasmacytic hyperplasia								
SH2015-137	49/M	PT	Axillary LN	+	ND	ND	Unknown	Unknown
SH2015-328	33/M	PT	Multiple LN sites	+	ND	ND	Rituximab	AWD

A/I, autoimmune or iatrogenic immunosuppression; ANED, alive no evidence of disease; AWD, alive with disease; BCR, B-cell receptor gene rearrangement; CHL, classical Hodgkin lymphoma; CNS, central nervous system; DOD, died of disease; EBER, Epstein-Barr virus–encoded small RNA; FISH, fluorescence in situ hybridization; HLH, hemophagocytic lymphohistiocytosis; IS, form of immunosuppression or background; LN, lymph node; ND, not done; PCR, polymerase chain reaction; PT, posttransplant; R, rituximab; RIS, reduction in immunosuppression; TCR, T-cell receptor gene rearrangement; +, positive; –, negative.

consistent oncogenic mutations or translocations in FH had not previously supported their inclusion. More recently, detailed cytogenetic analyses showed that a spectrum of clonal karyotypic abnormalities was demonstrable in PTLDs, including monomorphic PTLD (75%), polymorphic PTLD (33%), and FFH (11%).[13] The presence of cytogenetic abnormalities did not correlate with the type of PTLD, EBV infection, or clinical outcome measures and was detected in some cases where flow cytometry or polymerase chain reaction (PCR)–based studies did not demonstrate B-cell clonality.[13] A minority of patients with FFH subsequently developed more advanced forms of PTLD, typically after a long latency period.[14,15] The presence of clonal karyotypic abnormalities, together with the development of more aggressive and better-defined LPDs associated with immunodeficiency, at least in a subset of cases, supports the inclusion of FH as an immunodeficiency-related LPD.

The histologic features of FH in immunodeficiency and in immunocompetent patients cannot be reliably distinguished in most cases without the presence of EBV, particularly given the nonspecific characteristics and the absence of architectural effacement. Therefore, a high index of suspicion is necessary to consider testing for EBV-encoded small RNAs (EBER) in the appropriate clinical context.

Fourteen cases of FH, EBV+ were submitted to the workshop and included eight cases of PTLD, four cases arising in an autoimmune/iatrogenic setting, and two cases of unknown etiology presumably related to advanced age (Table 1). Among the eight PTLD cases, the patients ranged in age from 3 to 48 years, with a median age of 7 years. All patients had mass-forming lesions and showed enlargement of tonsils and adenoids in four cases, cervical lymphadenopathy in three cases, and generalized lymphadenopathy in one case. All biopsy specimens showed intact tissue architecture with prominent follicular hyperplasia and unremarkable interfollicular areas. All were EBER+, and one of six cases tested was also latent membrane protein 1 (LMP1)+. In addition, one of two cases tested showed the presence of a simple clonal immunoglobulin (IG) gene rearrangement. The distribution and number of EBER+ cells were variable and often localized to one or a few follicles with scant interfollicular EBER+ cells, as illustrated by case SH2015-123 (Drs Margolskee and Bhagat, Columbia University). This case was that of a 12-year-old boy, 8 years

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following cardiac transplantation, who was maintained on an immunosuppressive regimen of cyclosporine and azathioprine. He was EBV seronegative at the time of transplantation up until he presented with tonsillar hypertrophy. A bilateral tonsillectomy revealed FFH with a few EBER+ cells scattered within follicles and in interfollicular areas, but one isolated follicle showed increased numbers of EBER+ cells **Image 1**. Although flow cytometry, molecular PCR, and fluorescence in situ hybridization (FISH) studies did not detect B-cell clonality, minor clonal and nonclonal abnormalities were detected by G-band karyotyping. This case also illustrates the utility of EBER in situ hybridization in detecting EBV infection/reactivation in instances where EBV serology and viral load show no increase in EBV.

A subset of FH, EBV+ has been associated with concurrent or subsequent PTLD, some of which have also shown clonal evolution to a more aggressive PTLD.[14,16] Similarly, among the workshop cases, most cases of FH, EBV+ resolved spontaneously except in one patient (case SH2015-145, Drs Ewalt and Boyd, Stanford University), who subsequently developed a more aggressive PTLD. Case 145 was that of a child who received a heart transplant at age 2 years, developed FH, EBV+ at age 5 years, and a CHL, EBV+ (CHL-type PTLD) at age 9 years. A clonal relationship between the FH, EBV+ and the CHL, EBV+ was not demonstrable in that case.

Among the remaining six cases of FH, EBV+, four cases presented in the background of ulcerative colitis and primary sclerosing cholangitis (case SH2015-257), systemic lupus erythematosus (case SH2015-388), and dasatinib therapy (cases SH2015-219 and 330), whereas the cause was unknown in two cases and was presumed to be related to advanced age (case SH2015-214, 71 years and case SH2015-282, 65 years). Similar to FH in the posttransplant setting, all 11 cases were mass forming and showed FH with otherwise preserved tissue architecture. Four of six cases were EBER+ with a similar distribution of EBER+ cells localized primarily to one or more hyperplastic follicles; 2 of 3 cases showed positivity for LMP1, and both cases tested lacked EBV nuclear antigen 2 (EBNA2). In most of these cases, multiple lymph nodes were involved, including two cases that had widespread lymphadenopathy. Case SH2015-282 (Drs Soderquist and Frank, University of Pennsylvania) was that of a 65-year-old man with no known immunodeficiency who had multiple episodes of isolated lymphadenopathy at different sites occurring over a period of 5 years. Several lesions were biopsied over time and showed FH, EBV+; all resolved spontaneously without treatment.

Two cases were excellent examples of a recently recognized variant of FH, EBV+ occurring in association with dasatinib therapy, an oral tyrosine-kinase inhibitor administered to patients with chronic-phase or refractory chronic myeloid leukemia.[17,18] As illustrated in case SH2015-219 (Drs Ozawa and Gratzinger, Stanford University), the hyperplastic follicles showed involution of mantle zone cells into hyperplastic germinal centers and the formation of perivascular cuffs surrounding piercing capillaries, resembling some features of progressive transformation of germinal centers as well as hyaline-vascular Castleman disease. EBER+ cells were focal and confined to one follicle in case SH2015-219 and were absent in case SH2015-330. Case SH2015-330 further showed a clonal *IG* gene rearrangement. In both cases, the lymphoid proliferations resolved upon dasatinib withdrawal. An additional case (case SH2015-388, Dr Cogbill, Michigan) occurred in a 32-year-old woman with systemic lupus erythematosus who was treated with oral steroids and then hydroxychloroquine as her symptoms progressed. She developed widespread lymphadenopathy and splenomegaly accompanied by B symptoms, including fever and unintentional weight loss. Clinical features and laboratory values of multicentric Castleman disease (MCD) were present and associated with florid follicular and paracortical hyperplasia with interfollicular polytypic plasmacytosis. These examples expand the spectrum of previously recognized FH associated with immunodeficiency and indicate that variant patterns of FH may arise secondary to treatment with newer therapies such as dasatinib. Variant FH patterns also provide histologic changes that facilitate their detection even in the absence of EBV, as demonstrated by cases SH2015-330 and SH2015-388, where the associated morphologic changes were significantly atypical and essential in making the diagnosis.

Five additional cases of reactive B-cell hyperplasias that arose in the setting of primary immunodeficiency (three cases of chronic variable immunodeficiency [CVID], one case of autoimmune lymphoproliferative syndrome [ALPS], and one case of X-linked lymphoproliferative syndrome) were submitted to the workshop (cases SH2015-66, 84, 113, 229, and 239). All five cases showed a mass lesion with interfollicular expansion as well as FH but lacked EBV. One case (SH2015-239) showed an *IG* gene rearrangement. Given the difficulty in designating such lesions as FH related to immunodeficiency in the absence of EBV, such cases raise the need for a thorough workup for other causes of reactive hyperplasia, as well as the need for additional markers for recognizing reactive hyperplasias associated with immunodeficiency.

Infectious Mononucleosis-like Hyperplasia

IMHs are characterized by features that resemble infectious mononucleosis, including paracortical expansion by an immunoblast-rich infiltrate within a mixed background of T cells and plasma cells.[1] Like other hyperplasias, they form mass lesions with preservation of tissue architecture,

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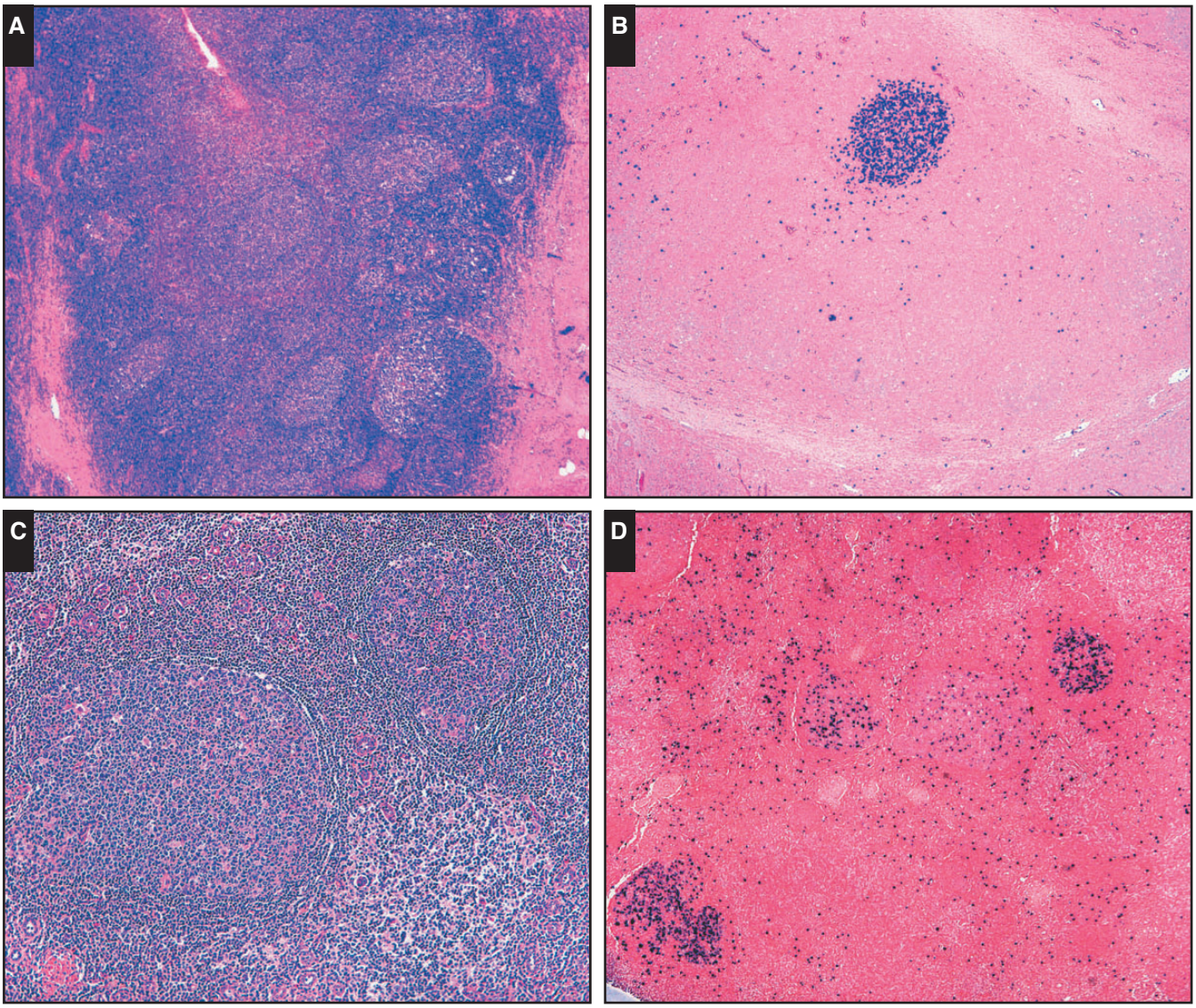

Image 1 Distribution of Epstein-Barr virus-encoded small RNA (EBER)–positive cells in follicular hyperplasias. Four case examples of follicular hyperplasia are illustrated. The distribution and number of EBER-positive cells were variable and often localized to one or a few follicles with scant interfollicular EBER-positive cells (case SH2015-123, **A** and **B** [x10], and case SH2015-145, **C** and **D** [x20]).

and most regress spontaneously or with withdrawal of the causative agent; rarely, they may be fatal. The histologic features of IMH are more distinctive than those of FH or PH because of the prominent immunoblastic component in IMH, which permits the diagnosis of IMH even in the absence of EBV. Differential diagnostic considerations include other reactive and neoplastic conditions with increased immunoblasts such as infectious mononucleosis; polymorphic B-cell LPDs (B-LPDs), particularly mucocutaneous ulcer; and EBV+ CHL.

Nine cases of IMH were submitted to the workshop, including five that occurred in the posttransplant setting and four others in autoimmune/iatrogenic settings. The cases ranged in age from 3 to 61 years (median, 20 years). Eight of nine cases were associated with EBV (EBER+). Among the PTLD cases, three had tonsillar/adenoid enlargement while the remaining two had widespread lymphadenopathy. The overall architecture was preserved in the involved lymph nodes and tonsils, and although some hyperplastic follicles were present in most cases, there was marked interfollicular expansion by a mixed infiltrate composed of immunoblasts, some of which resembled Hodgkin/Reed-Sternberg (HRS)–like cells, small T cells, and plasma cells. EBER+ cells showed a variable distribution and ranged from scattered to numerous interfollicular cells or involved both follicular and interfollicular compartments. EBV latency was also variable (one of four LMP1 positive; zero of

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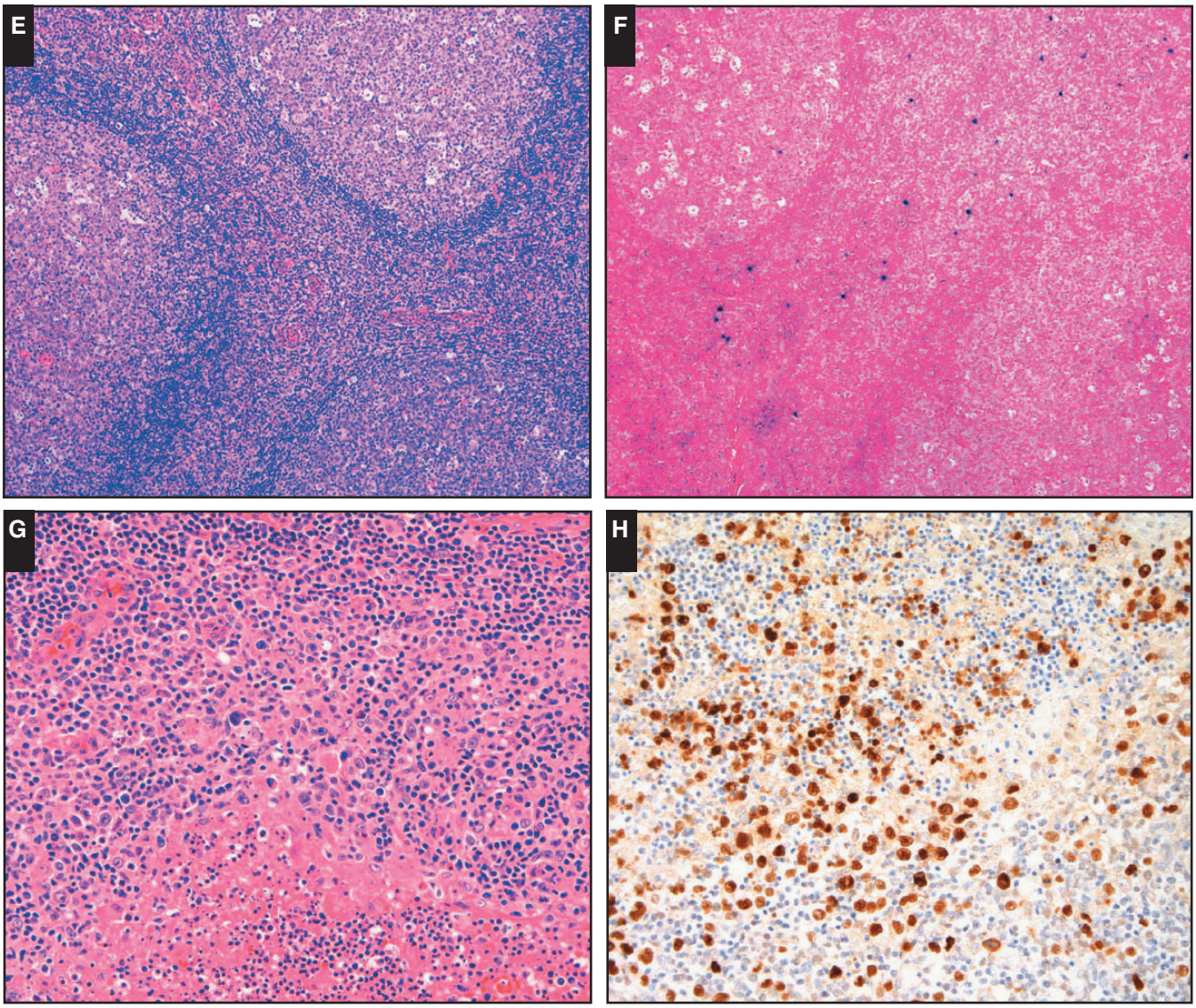

Image 1 (cont) Some cases showed few EBER-positive cells scattered within interfollicular areas (case SH2015-268, **E** and **F** [x40]), whereas others showed an intense infiltrates of EBER-positive cells (case SH2015-282, **G** and **H** [x60]).

one EBNA2 positive). Small clonal *IG* gene rearrangements have been reported in IMH in the literature[19,20]; two of six workshop cases demonstrated a clonal *IG* gene rearrangement (case SH2015-158, Dr McPhail, Mayo Clinic; case SH2015-77, Dr Felgar, Pittsburg). Although reported in occasional cases in the literature, none of the three cases tested showed a clonal T-cell gene rearrangement. Similarly, simple clonal karyotypes have been reported[13]; however, karyotypes were not available for the workshop cases.

Of the four non-PTLD patients who had IMH, three had a history of autoimmune disease treated with immunomodulatory therapies, whereas the fourth patient was placed on maintenance methotrexate following chemotherapy for B-lymphoblastic leukemia. Three patients had multiple sites of lymphadenopathy, whereas one patient had involvement of the adenoids, lungs, and the central nervous system (CNS). The histologic features and EBV involvement were similar to the cases of IMH arising in the posttransplant setting. None of the nine IMH cases were associated with concurrent or subsequent progression to more aggressive disease, although one case, which was associated with Still disease and demonstrated hemophagocytic lymphohistiocytosis, was fatal (case SH2015-456, Dr Gerbi, Detroit).

Of relevance is the difficulty of identifying an etiologic factor in patients with multiple comorbidities: one case that exemplified this issue (case SH2015-163, Dr Daphne de Jong, Netherlands) was from a 20-year-old woman with complex autoimmune syndrome with minimal change nephropathy, anterior uveitis, Raynaud syndrome, arthralgia, and multiple sclerosis who had been treated with various

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immunosuppressive therapies, including steroids, cyclosporine, and an α-4 integrin antagonist (natalizumab). Given the longstanding autoimmune conditions and use of several iatrogenic agents, the IMH lesions in this patient posed a challenge for clinical management as the specific predisposing condition or agent could not be determined.

Separation of IMH from EBV+ mucocutaneous ulcer, polymorphic B-LPD, and CHL can be challenging. The distribution of lesions in mucosal and cutaneous sites, together with their circumscription, are the most salient features that allow the separation of mucocutaneous ulcer from IMH. Polymorphic B-LPDs, in contrast to IMH, are destructive lesions that exhibit a full range of B-cell maturation stages and typically harbor clonal B-cell gene rearrangements. Although CHL in immunodeficiency settings must fulfill criteria for the diagnosis of CHL and is generally associated with architectural effacement, its separation from IMH may be complicated because B-cell gene rearrangement studies are not informative in either diagnosis. In instances where architectural effacement may not be readily appreciable, such as in needle core biopsy specimens, distinguishing IMH from CHL, EBV+ may pose additional challenges. Similarly, separation from diffuse large B-cell lymphoma (DLBCL), EBV+ may be difficult when there is a T-cell/histiocyte-rich background and absence of sheets of EBV-positive large cells. Although B-cell receptor gene rearrangement studies are helpful to separate polymorphic B-LPDs and lymphomas from hyperplasias, limited B-cell repertoires in small biopsy specimens or in EBV-driven proliferations may yield spurious clones and further confound accurate diagnoses.

Plasmacytic Hyperplasia

PH is morphologically characterized by the predominance of plasma cells expanding the medullary cords and extending to involve the interfollicular regions.[1] Immunoblasts are generally infrequent, although follicular hyperplasia may be present. The plasma cells are polytypic and not expected to harbor B-cell receptor gene rearrangements. As in FH and IMH, most cases of PH involve the tonsils and adenoids of younger patients and are rarely associated with concurrent or subsequent polymorphic B-LPDs or lymphomas. Similar to FH, the histologic features are nonspecific, and the presence of EBV is imperative for the diagnosis.

Two cases of PH, both occurring in the posttransplant setting, were submitted to the workshop. In contrast to the tonsillar/adenoid involvement reported in the literature, one patient had isolated lymphadenopathy, whereas the other had multifocal lymphadenopathy. Both cases showed interfollicular expansion by polytypic plasma cell proliferations, which were associated with EBV (EBER+). Variable numbers of hyperplastic follicles were also present (case SH2015-328, Dr Bradley, Emory University). Neither of the workshop cases was associated with clonal proliferations or with progression of disease. PH lesions occurring in other immunodeficiency settings such as in the elderly have been reported[21]; however, none were submitted to this workshop. Two additional cases of EBV-negative, mass-forming lesions of polytypic plasma cell proliferations were submitted to the workshop. Case SH2015-467 (Dr Qayyum, Children's Hospital of Philadelphia) occurred in a 24-year-old woman with CVID who had three mass lesions involving the brain parenchyma. Case SH2015-248 (Dr Yohe, University of Minnesota) occurred in an inguinal lymph node of a 6-year-old male following hematopoietic stem cell transplant. As with EBV-negative FH, it was not possible to classify these latter two cases as PH associated with immunodeficiency.

In summary, the cases of hyperplasias submitted to the workshop occurred in different types of immunodeficiency settings and shared several characteristic features. They typically formed mass lesions with nondestructive growth such that the involved tissue architecture was preserved. Clinical presentations were variable and included adenotonsillar enlargement that typically occurred in children in the posttransplant setting, isolated lymph node enlargement, involvement of multiple concurrent or metachronous nodal sites, or widespread lymphadenopathy. EBV involvement was also variable, with EBER+ cells typically focal and localized to one or a few hyperplastic follicles in FH to scattered or numerous EBER+ cells in the interfollicular areas in FH, IMH, and PH. The salient histologic features for the diagnosis of FH, IMH, and PH are summarized in **Figure 1**. Association with EBV was an important feature to identify hyperplasias, particularly FH and PH, in immunodeficiency settings since other distinguishing histologic features were nonspecific. Separation from other reactive (infectious or inflammatory) causes of hyperplasia was not possible in the absence of EBV. As reported in the literature, most of the cases were self-limiting, although a small minority of cases had subsequent development of more aggressive lymphoproliferative disorders or lymphomas. Occasional simple clonal IG rearrangements or karyotypes were also identified, and although these features did not lead to a worse outcome, one case with hemophagocytic lymphohistiocytosis was fatal.

Polymorphic B-LPDs (Polymorphic PTLD and Polymorphic PTLD-Like Lesions in Other Immunodeficiency Settings)

Polymorphic B-LPDs are broadly defined as morphologically polymorphous lesions that efface the architecture

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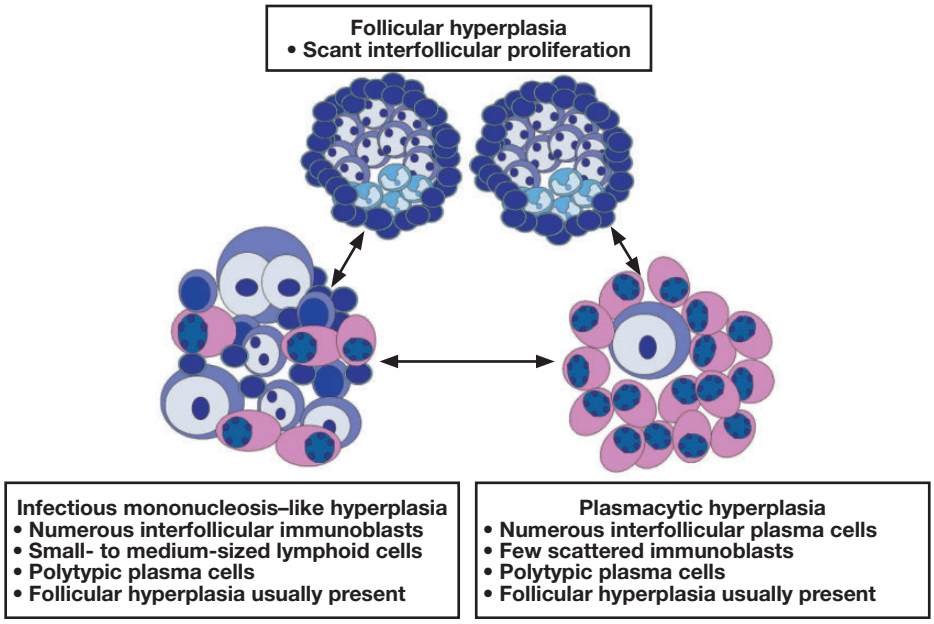

Figure 1 Histologic features of B-cell hyperplasias in immunodeficiency settings. The cartoon illustrates the relationship among the three types of hyperplasias. There is retention of hyperplastic follicles in all types. Interfollicular proliferation ranges from scant in follicular hyperplasia, to a mixed inflammatory infiltrate with increased immunoblasts in infectious mononucleosis-like hyperplasia, to one that is rich in polytypic plasma cells in plasmacytic hyperplasia.

of the involved tissue site or cause destructive masses but do not fulfill criteria for the diagnosis of lymphoma.[1,11,13,14,22] They are classified in the posttransplant setting as polymorphic PTLD or P-PTLD but also occur in other immunodeficiency settings. P-PTLDs account for 20% to 80% of PTLDs and are the most common PTLDs in the pediatric age group.[23] We adopted the term *polymorphic B-lymphoproliferative disorder* in an effort to include P-PTLD as well as P-PTLD–like lesions in other immunodeficiency settings.

Most polymorphic lesions are clonal proliferations driven by EBV that typically lack additional genetic alterations and regress in response to reduction in immunosuppression. They demonstrate variable proportions of B and T cells; B cells typically exhibit a full range of B-cell maturation stages from small- to medium-sized lymphocytes, plasma cells, and immunoblasts. The number and cytologic features of admixed immunoblasts may be variable and include atypical forms that mimic HRS-like cells. In some cases, T cells and histiocytes may predominate. Although polymorphic B-LPD almost always shows clonal B-cell receptor gene rearrangement, immunoglobulin light chain expression is often variable and ranges from polytypic to light chain–restricted B cells and plasma cells. Some lesions may show focal clonal proliferations or different light chain–restricted B cells and plasma cells in different portions of the same biopsy specimen. Simple karyotypic abnormalities may be demonstrable and have been reported in 15% to 30% of polymorphic B-LPDs.[12,13] Given the morphologic and immunophenotypic spectrum of polymorphic B-LPD, defining the boundaries of this entity is often challenging. The differential diagnosis is therefore broad and not only encompasses nondestructive lesions such as hyperplasias, particularly IMH and EBV+ mucocutaneous ulcer, but also includes lymphomas such as CHL; plasmablastic lymphoma; lymphomatoid granulomatosis; large B-cell lymphomas, particularly T-cell and histiocyte-rich large B-cell lymphoma; and T-cell LPD/lymphoma, particularly angioimmunoblastic T-cell lymphoma.

Polymorphic B-LPDs were the single largest category of cases submitted to the workshop and included 38 cases occurring in various immunodeficiency settings as summarized in **Table 2**. Polymorphic B-LPDs occurring in the posttransplant and primary immunodeficiency settings were the most frequent (10 each), followed by autoimmune/iatrogenic settings (n = 8), human immunodeficiency virus (HIV) (n = 6), and an unknown cause presumably related to immune senescence (n = 4). They affected all ages (1-90 years; median, 51 years). Unlike those reported in the literature, only five of 38 cases occurred in children. All except one case was associated with EBV, and an additional case showed multiple sites of involvement where EBV was present in one biopsied site but not the other. The clinical presentation ranged from isolated lymphadenopathy (n = 7) to widespread lymphadenopathy with or without splenomegaly (n = 7),

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Table 2
Clinicopathologic Features of Polymorphic B-Lymphoproliferative Disorders Submitted to the Workshop

Case No.	Sex/Age, y	IS	Site	EBV	PCR	IG Light Chain	Cyto/FISH	Treatment	Outcome
SH2015-13	1/M	PT	Multiple LN sites	+	BCR+	Polytypic	46,XY	RIS	ANED
SH2015-35	44/M	PT	Inguinal LN	+	ND	λ	ND	DLI and R	ANED
SH2015-125	62/M	PT	Lung nodules	+	ND	Polytypic	ND	Unknown	Unknown
SH2015-133	32/M	PT	Nasal polyp, bowel	+	BCR–TCR–	ND	ND	Unknown	Unknown
SH2015-236	51/M	PT	CNS	+	ND	ND	ND	Unknown	Unknown
SH2015-240	25/M	PT	Lung mass	+	BCR+	κ	BCR+	Unknown	ANED
SH2015-340	14/F	PT	Cervical LN	–	BCR+TCR–	λ	ND	Unknown	Unknown
SH2015-404	51/F	PT	Colon, BM	+	TCR+	λ	ND	Steroids	DOD
SH2015-460	55/M	PT	Inguinal LN	+	ND	κ	ND	RIS	ANED
SH2015-461	19/F	PT	Lung nodule	+	BCR+	λ	–	Rituxan	AWD
SH2015-80	45/M	A/I	Cervical LN	+	ND	Polytypic	ND	Unknown	Unknown
SH2015-171	51/F	A/I	Multiple LN sites	+	ND	ND	ND	R-chemotherapy	DOD
SH2015-184	74/F	A/I	Multiple LN sites	+	ND	κ	ND	RIS	ANED
SH2015-194	61/F	A/I	Cervical LN	+	ND	λ	46,XX	Unknown	ANED
SH2015-272	63/F	A/I	Lung mass	+	BCR–TCR–	Polytypic	Complex	Unknown	DOU
SH2015-408	61/M	A/I	Bilateral lung	+	BCR+	κ	ND	Rituxan	DOD
SH2015-428	60/F	A/I	Cervical LN	+	ND	Polytypic	ND	Cytoxan, steroids	ANED
SH2015-478	52/F	A/I	Multiple LN sites	+	BCR+	Polytypic	ND	RIS	ANED
SH2015-301	12/F	PID	CNS	+	ND	ND	ND	HSCT	ANED
SH2015-314	27/M	PID	Cervical LN, spleen	+	BCR–	Polytypic	ND	R-chemotherapy, HSCT	ANED
SH2015-392	27/F	PID	Multiple sites	+	BCR+TCR–	κ/λ	Hyperdiploid	Rituximab	ANED
SH2015-418	27/M	PID	Lung nodules	+	BCR–TCR–	NA	ND	Unknown	Unknown
SH2015-434	32/F	PID	Spleen, BM	+	BCR–TCR+	Polytypic	46,XX	Splenectomy	Unknown
SH2015-507	26/F	PID	Multiple LN sites	+	ND	ND	ND	R-chemotherapy	ANED
SH2015-70	57/M	HIV	Nose, liver	+	ND	ND	ND	HAART	ANED
SH2015-83	40/F	HIV	Bilateral lung	+	BCR+	Polytypic	ND	HAART	ANED
SH2015-187	?/M	HIV	Cervical LN	+	BCR–TCR+	Polytypic	ND	HAART, R-CHOP	ANED
SH2015-211	26/M	HIV	CNS	+	BCR+TCR–	ND	46,XY	HAART	AWD
SH2015-215	52/M	HIV	CNS	+	ND	Polytypic	ND	Unknown	Unknown
SH2015-246	30/M	HIV	Rectum	+	ND	ND	ND	Unknown	AWD
SH2015-124	83/F	None	LN, tonsil	+	BCR–	ND	ND	Rituximab	ANED
SH2015-132	90/F	None	LN, skin	+	BCR+TCR–	ND	ND	Unknown	Unknown
SH2015-188	67/F	None	Spleen, BM	+	ND	Polytypic	46,XX	Rituximab	ANED
SH2015-511	64/M	None	Cervical LN	+	BCR–	Polytypic	ND	Chemotherapy	ANED

A/I, autoimmune or iatrogenic immunosuppression; ANED, alive no evidence of disease; AWD, alive with disease; BCR, B-cell receptor gene rearrangement; BM, bone marrow; CNS, central nervous system; DLI, donor lymphocyte infusion; DOD, died of disease; DOU, died of unrelated cause; EBV, Epstein-Barr virus; FISH, fluorescence in situ hybridization; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IS, form of immunosuppression or background; LN, lymph node; ND, not done; PCR, polymerase chain reaction; PID, primary immunodeficiency; PT, posttransplant; R, rituximab; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; RIS, reduction in immunosuppression; TCR, T-cell receptor gene rearrangement; +, positive; –, negative.

as well as involvement of extranodal sites (n = 21), including the lungs (n = 6), CNS (n = 5), and skin (n = 2). Several patients demonstrated extensive systemic symptoms, and two were associated with hemophagocytic lymphohistiocytosis (HLH). Unlike reports in the literature, only 53% of polymorphic B-LPDs among the workshop cases showed *IG* gene rearrangements; occasional cases with small T-cell clones and simple clonal karyotypes were seen. Light chain expression was variable and polytypic in 58% of cases. Most patients required treatment, and a wide range of treatment options were employed, including withdrawal of immunosuppression, institution of antiretroviral therapy in patients with HIV, donor-lymphocyte infusion, rituximab with or without a variety of chemotherapeutic agents and/or steroids, chemoradiotherapy, and hematopoietic stem cell transplantation. Clinical outcomes were also variable, with resolution of symptoms with withdrawal of immunosuppression to death due to dissemination of disease, multiorgan failure, and infectious complications in three cases.

The 10 P-PTLD cases occurred in the background of solid organ as well as hematopoietic stem cell transplantation and ranged in age from 1 to 62 years with a median age of 38 years. These lesions frequently followed primary EBV infection where the recipient was EBV negative at the time of transplantation. Lymph nodes were involved in three cases, both nodal and extranodal sites in one case, and extranodal sites in six cases, including lungs (n = 4), CNS (n = 1), colon (n = 1), nasal polyp (n = 1), bone (n = 1), and liver/spleen (n = 1).

Histologic features showed the presence of architectural destruction and a mixed infiltrate with full range of B-cell maturation stages represented, including immunoblasts, small- to medium-sized lymphoid cells, plasma cells,

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and variable numbers of reactive T cells. The immunoblasts were typically numerous and showed atypical forms and HRS-like morphology. The HRS-like cells were characterized by the expression of CD45, CD20/CD79a, CD30, PAX5, OCT2, and BOB1, as well as CD15 in a subset. In some cases, T cells were the predominant cell type within the infiltrate. EBER was positive in nine of 10 cases, whereas LMP1 (three of five) and EBNA2 (one of two) were positive in subsets of cases.

A typical example of polymorphic B-LPD was provided by case SH2015-13 (Dr Song, UCLA), which occurred in a 14-month-old boy after cardiac transplantation who had persistent fever, pancytopenia, rising EBV titers, and extensive lymphadenopathy in bilateral cervical, mediastinal, and left abdominal para-aortic regions as well as hematosplenomegaly. An excisional lymph node biopsy specimen and the bone marrow showed effacement by an extensive polymorphic infiltrate with numerous EBER+ immunoblasts. Flow cytometry identified a large B-cell proliferation lacking light chain expression. Both biopsy specimens demonstrated an identical clonal *IG* gene rearrangement, but no karyotypic or FISH abnormalities were detected. In addition, six of eight laboratory criteria for the diagnosis of HLH were met, including numerous bone marrow histiocytes that demonstrated hemophagocytosis. The patient was treated with reduction of immunosuppression, etoposide, and dexamethasone, with complete resolution of the P-PTLD.

Among the P-PTLDs, the mixed or polymorphous nature of the infiltrates resulted in varied appearances not only between cases but also in different biopsy specimens from the same patient as seen in case SH2015-133 (Dr Maietta, Montreal University) and within the same biopsy specimen (case SH2015-460, Dr Tousseyn, Leuven). Case SH2015-133 was from a 32-year-old man, 6 years after lung transplant who had polymorphic B-LPD in two separate sites: a nasal polyp characterized by a mixed infiltrate with prominent HRS-like cells and a small intestinal lesion with numerous immunoblasts but without prominent HRS-like morphology. In case SH2015-460, an inguinal lymph node in a 55-year-old patient after allogeneic hematopoietic stem cell transplant showed two distinct components: one resembling a polymorphous lesion with immunoblastic proliferation and HRS-like cells and the other a relatively monomorphic plasmablastic proliferation with brisk mitotic activity resembling a plasmablastic lymphoma. Both components were EBER+.

Polymorphic B-LPDs are characterized by the presence of clonal *IGH* gene rearrangements. Among the workshop cases, three of five showed clonal *IGH* gene rearrangements; six of seven demonstrated at least focal light chain restriction, although some demonstrated different light chains in different portions of the biopsy specimen. One case showed a small T-cell gene rearrangement. None of the cases demonstrated a clonal karyotype. In six patients in whom clinical outcome was reported, four were alive with no evidence of disease, while another showed progressive disease despite rituximab treatment. One patient died of disseminated disease involving the colon, bone marrow, and multiorgan failure.

Ten cases of polymorphic B-LPDs occurred in the setting of primary immunodeficiency, including six patients with CVID and one each with dedicator of cytokinesis 8 (DOCK8) deficiency, Chediak-Higashi syndrome, X-linked lymphoproliferative syndrome, and Bloom syndrome. Clinicopathologic, histologic, and molecular features were similar to the spectrum presenting in the posttransplant setting with a median age of presentation of 26.5 years. Two of the five cases tested showed a clonal IGH rearrangement and light chain restriction, and one of three showed small T-cell clones and another showed an oligoclonal proliferation. One case showed a hyperdiploid karyotype. Treatment was highly variable, ranging from rituximab, chemotherapy, and hematopoietic stem cell transplant. Where available, outcomes usually showed resolution of the polymorphic B-LPD, although two patients subsequently developed CHL and DLBCL, both associated with EBV.

The eight polymorphic B-LPD cases occurring in autoimmune/iatrogenic settings displayed some similarities as well as differences from the P-PTLD group. The patients were typically older adults and ranged in age from 45 to 74 years with a median of 60.5 years. They arose most commonly (five of eight) in patients with rheumatoid arthritis treated with methotrexate or other similar immunosuppressive regimen. Similar to P-PTLD, they occurred in a single nodal site (three of five), multiple nodal sites (three of five), or extranodal sites such as the lung (two of five). *IGH* gene rearrangements were present in two of four cases and three cases each showed polytypic or light chain–restricted B and plasma cells. One case showed a clonal karyotypic abnormality.

Management of these lesions varied from withdrawal of immunosuppression to single-agent rituximab or in combination with cytoxan, steroids or immunochemotherapy, and hematopoietic stem cell transplant. Clinical outcome data were available for seven patients, of whom four achieved complete remission, two died of progressive disease, and another patient died of an unrelated cause (pancreatic carcinoma). Two cases exemplifying typical scenarios in the autoimmune/iatrogenic background were discussed in further detail. The first case was from a 61-year-old man with progressive anemia and fatigue who had multiple bilateral pulmonary nodules without lymphadenopathy or hepatosplenomegaly (case SH2015-408, Dr Perry, Manitoba). At

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age 19 years, he was diagnosed and treated for CHL with combination chemoradiation. He had a recurrence but again achieved complete response. His disease course was complicated by anthracycline-based cardiotoxicity and development of a polymorphic B-LPD, EBV+ for which rituxan monotherapy was planned, but the patient died of deteriorating cardiorespiratory function. The second case was from a 52-year-old woman with rheumatoid arthritis who was managed on an immunosuppressive regimen of methotrexate and tumor necrosis factor α (TNF-α) inhibitor (case SH2015-478, Drs Wu and Johnson, Stanford University). She developed multiple sites of lymphadenopathy associated with B symptoms, and a cervical lymph node demonstrated polymorphic B-LPD, EBV+. The mixed lymphoid proliferation showed large atypical cells resembling HRS cells, and the differential diagnostic considerations included an EBV+ CHL as well as large B-cell lymphoma. Her symptoms presented 1 month after cessation of immunosuppression and eventually resolved completely.

In autoimmune diseases such as rheumatoid arthritis, disease severity by itself has been linked to the development of EBV-associated LPD and lymphoma. In addition, the duration of disease as well as the length of treatment with an immunosuppressive regimen such as methotrexate has also been associated with the development of immunodeficiency disorders. These proliferations can also arise after an interval of methotrexate withdrawal at the time of reintroduction of the drug, further complicating the management of such patients. Most cases in the literature are associated with rheumatoid arthritis and methotrexate; however, several autoimmune conditions as well as therapeutic agents such as TNF-α and integrin antagonists have been implicated in the genesis of the immunodeficiency-related spectrum of lymphoproliferations.[24-30] These cases of immunodeficiency-related polymorphic B-LPDs arising in autoimmune/iatrogenic conditions submitted to the workshop underscored the need for a high index of suspicion to obtain additional clinical information in circumstances where the pathologist may not be made aware of prior treatment regimens or the treatment course and timing.

Six cases of polymorphic B-LPDs occurred in the HIV/AIDS setting and four additional cases in older individuals likely related to immune senescence. Clinicopathologic, histologic, and molecular features were similar to the spectrum presenting in posttransplant settings. Median ages of presentation included 35 years for HIV/AIDS and 75 years for those associated with immune senescence. Most cases tested showed a clonal IGH rearrangement, occasional small T-cell clones, and polytypic light chain expression patterns; none showed a clonal karyotype.

In contrast to the typical aggressive lymphomas that occur in patients with HIV/AIDS, such as primary effusion lymphoma, plasmablastic lymphoma, and large B-cell lymphoma arising in human herpesvirus 8 (HHV8)–associated MCD, six workshop cases showed polymorphic B-LPDs. Four of six patients had not been previously treated with highly active antiretroviral therapy (HAART) at the time of diagnosis of the polymorphic B-LPD, and another was on HAART but showed poor compliance. Four of six patients showed improvement or complete resolution of symptoms after initiation of HAART; another patient required R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) in addition to HAART and achieved complete remission. **Image 2** illustrates a case of polymorphic B-LPD presenting as bilateral pulmonary nodules with radiologic features initially diagnosed as primary tuberculosis in a patient with HIV/AIDS who showed a dramatic response of the LPDs after initiation of HAART (case SH2015-83, Dr Goodlad, Edinburgh).[31]

In summary, the cases of polymorphic B-LPDs submitted to the workshop showed a broad clinicopathologic spectrum, occurred in multiple different immunodeficiency settings, and elicited a broad differential diagnosis. Typical features included effacement and destructive growth in nodal or extranodal sites and a full spectrum of B-cell maturation stages admixed with abundant immunoblasts, often with HRS-like morphology and a mixed inflammatory infiltrate. These lesions raised the need to broaden differential diagnostic considerations as well as obtain additional ancillary studies, including quantitative immunoglobulin profiles, to confirm the possibility of immunodeficiency-associated polymorphic B-LPDs that may resolve with conservative management. Most patients required some form of clinical intervention, and a graded approach to management was found to be efficacious, with aggressive treatment regimens reserved for patients with refractory disease. Marked responses were observed in patients with autoimmune/iatrogenic immunosuppression after withdrawal of immunosuppressive agents and in patients with HIV/AIDS, in whom complete resolution was achieved after initiation of HAART. The HIV/AIDS examples of polymorphic B-LPDs underscored the need for a trial of conservative management in patients with lesions that mimic aggressive lymphomas such as CHL or large B-cell lymphoma in the background of immunosuppression. Polymorphic B-LPDs arising in autoimmune/iatrogenic conditions emphasized the need for a high index of suspicion to obtain clinical history of prior or current treatment regimens. Patients with underlying primary immunodeficiency may be at higher risk for developing additional immunodeficiency-related LPDs and thus must be monitored closely even if the initial polymorphic LPD has resolved.

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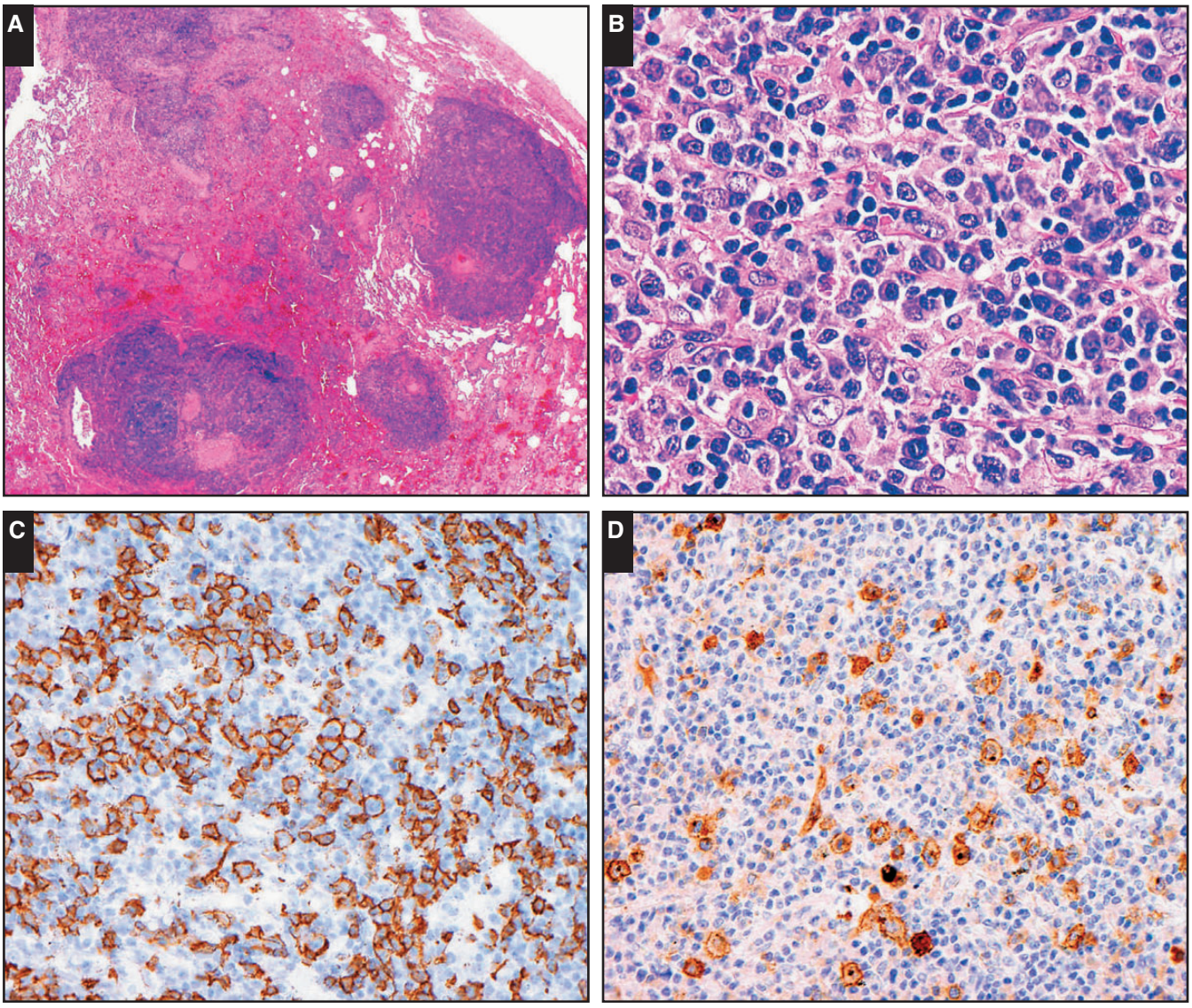

Image 2 Polymorphic B-lymphoproliferative disorder in a patient with human immunodeficiency virus (HIV) (case SH2015-83). Initially diagnosed as primary tuberculosis, this polymorphic B-lymphoproliferative disorder presented as bilateral pulmonary nodules in a 40-year-old woman with HIV (**A**, x4). A polymorphous infiltrate with increased immunoblasts is seen in the lung biopsy specimen (**B**, x40), which shows expression of CD20 (**C**, x40) and CD30 (**D**, x40),

EBV-Positive Mucocutaneous Ulcer

EBV-positive mucocutaneous ulcer was first described as an entity in 2011, although it is likely that descriptions of similar lesions were present in earlier or contemporaneous literature.[32-35] Using our proposed nomenclature, this entity will be further referred to as mucocutaneous ulcer (MCU), EBV+. The initial series included a majority of apparently immunocompetent but elderly individuals, patients receiving therapeutic immunosuppression for rheumatoid arthritis and other autoimmune disorders, and one allogeneic stem cell transplant recipient.[32] A small number of cases have subsequently been reported, including some after solid organ transplant.[36-40] In cases of iatrogenic immunosuppression-associated MCU, EBV+ outside the transplant setting, methotrexate is the most commonly implicated drug, usually in the context of a connective tissue disorder such as rheumatoid arthritis, although associations with azothioprine and cyclosporine have also been documented.[32,33,35-37,39,40] MCU, EBV+ also appears to be one of the more common subtypes of EBV-associated lymphoproliferative disorder arising as a complication of methotrexate therapy, accounting for around 40% of cases.[37]

Patients have well-circumscribed, often painful, ulcerating lesions arising at mucosal or cutaneous sites. Oropharyngeal

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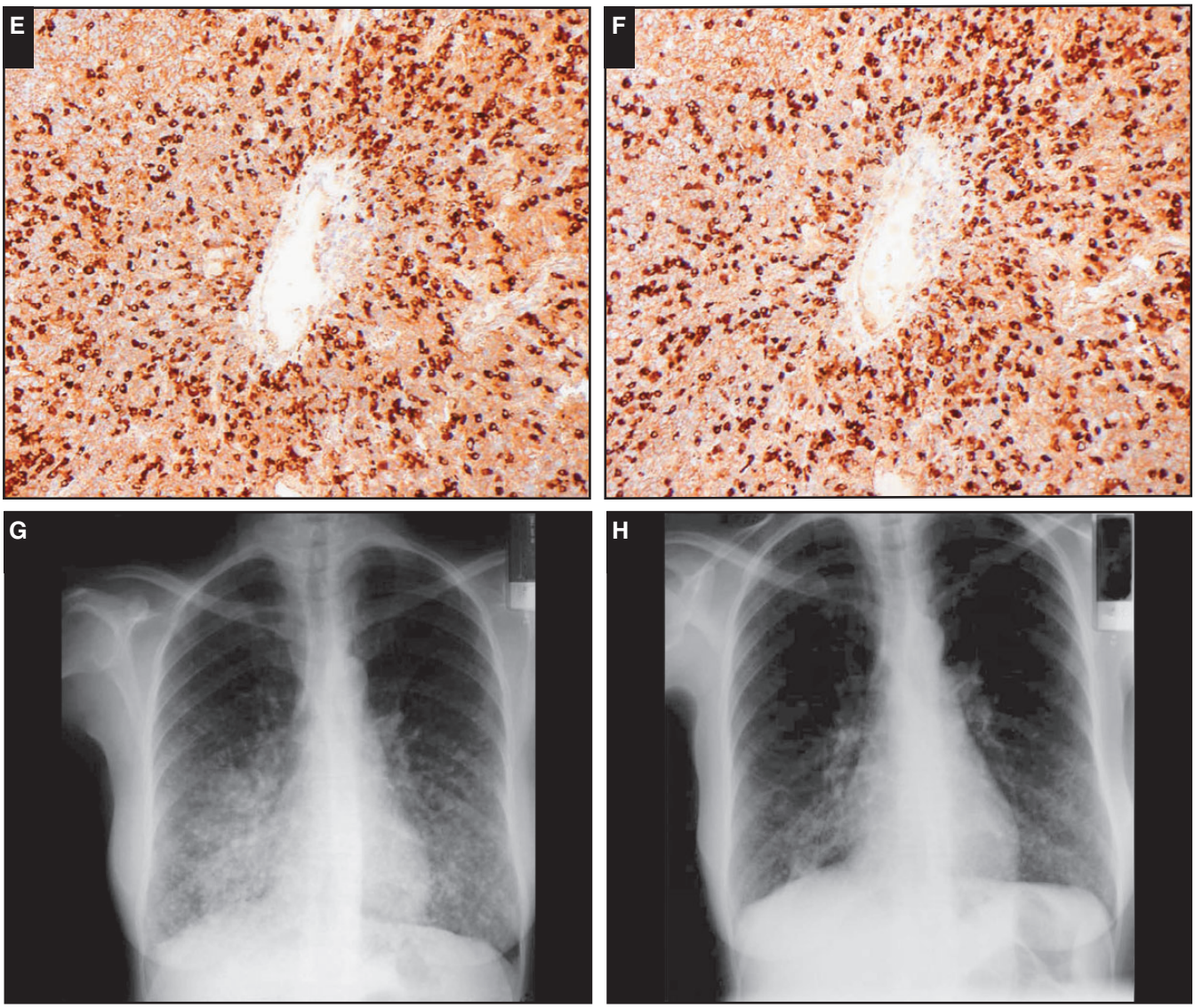

Image 2 (cont) Also shown are expression of polytypic κ (**E**, x40) and λ (**F**, x40) light chains. Radiographic images taken at initial presentation (**G**) and after initiation of highly active antiretroviral therapy (**H**) show dramatic improvement of the pulmonary infiltrates.

mucosa is the most frequent site of presentation.[32,34,37] Cutaneous involvement is often perioral, but other acral sites or the trunk may be affected. Any part of the gastrointestinal tract may be involved, and patients occasionally have a variety of abdominal symptoms, including abdominal emergencies.[38] Importantly, and irrespective of site, no mass lesion is detectable on clinical examination or imaging.[38] The presence of systemic lymphadenopathy and/or splenomegaly should also lead to a presumptive diagnosis of MCU, EBV+ being questioned. Two cases with concomitant cervical lymphadenopathy local to MCU, EBV+ of the tonsil were included in the initial study, but as these were not examined microscopically, it is possible that the enlarged nodes were reactive in nature.[32] In addition, EBV-DNA is typically undetectable in peripheral blood, in contrast to many other types of EBV-associated lymphoproliferative disorders.[38]

Biopsy specimens of MCU, EBV+ reveal circumscribed shallow ulcers, the base of which contains a polymorphous infiltrate comprising variable numbers of immunoblasts and large atypical Reed-Sternberg–like cells. These are admixed with small lymphocytes, plasma cells, histiocytes, and eosinophils. Plasmacytoid apoptotic cells are usually prominent, and there is vascular invasion with thrombosis and sometimes necrosis in a significant proportion.[32] The base of the lesion is sharply defined by a rim of small lymphocytes. In squamous mucosa and skin, there

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may be reactive epithelial atypia, and pseudoepitheliomatous hyperplasia is often present.[32,38] The immunoblasts and Reed-Sternberg–like cells are EBV-positive B-cells that are uniformly CD30 positive. A proportion show downregulation of CD20, but they express PAX5, MUM1, OCT2, and, usually, BOB1.[32,38] A high prevalence of CD15 expression was reported in one study but was absent in another.[32,38] Staining for EBV typically reveals a type II or type III latency pattern.[32,37,38] The background small lymphocytes and some activated cells are of T lineage, and antibodies to CD3 are useful in highlighting the constraining rim of T lymphocytes at the base and sides of each lesion. Monoclonal immunoglobulin gene rearrangement can be identified in around half of cases.[32,34,38]

The pathogenesis of EBV-MCU is not fully established. In immunocompetent individuals, cytotoxic T cells act to keep EBV-induced B-cell proliferation in check and maintain the virus in a dormant state. A diminished T-cell repertoire is encountered in immunosuppressed patients, conferring a reduced ability to detect all EBV-associated antigens, with consequent proliferation of only restricted clones of EBV-specific T cells when the virus is encountered. In MCU, EBV+, it is speculated that immune surveillance is reduced, either as a result of age-related immune senescence or iatrogenic immunosuppression, to a level that is only just sufficient to maintain the virus in a dormant state systemically. Exposure to an additional site-restricted immune-modulating factor is then believed to tip the balance toward a localized EBV-driven lymphoproliferation.[32] Sites at which EBV-infected cells are prevalent, such as Waldeyer's ring, may be particularly prone to this disruption in equilibrium. This hypothesis may also explain the high incidence of clonal and oligoclonal T-cell receptor gene rearrangements found in lesions of MCU, EBV+.[34,41-43]

MCU, EBV+ is an indolent disease. Prior to the initial series, cases were often treated aggressively. However, in apparently immunocompetent elderly individuals, spontaneous regression appears to be the norm, while reduction in immunosuppression is sufficient for most patients receiving therapeutic immunosuppression.[32-36,38,40,44] Most patients do not have a relapse, although occasional cases run a relapsing and remitting course without progression.[32]

The differential diagnosis of MCU, EBV+ includes EBV-positive cases of polymorphic B-cell lymphoproliferative disorder, DLBCL, and CHL. The cytologic composition and phenotype of MCU, EBV+ is indistinguishable from polymorphic B-LPD in many cases and in some is identical to DLBCL, EBV+. Clinical features are paramount in making the distinction, particularly the localized nature of MCU, EBV+ and absence of a mass lesion. Peripheral blood EBV-DNA load may also be useful, and a putative diagnosis of MCU, EBV+ should be questioned if elevated.[38] Pathologically, the sharp circumscription of MCU, EBV+ with a band of small T cells at the base of the lesion should help differentiate from the more infiltrative pattern seen with polymorphic B-cell lymphoproliferative disorders and EBV-positive DLBCLs. MCU, EBV+ may also resemble CHL, morphologically and phenotypically, with the Reed-Sternberg–like cells expressing CD30 and CD15. However, the clinical criteria described above, the extreme rarity of CHL presenting as extranodal disease in the absence of nodal involvement, and the presence of an intact B-cell program with CD45 expression in MCU, EBV+ should allow distinction.

A total of 17 cases submitted to the workshop **Table 3** fulfilled criteria for MCU, EBV+: five cases in apparently immune-competent individuals (cases SH2015-1, 72, 299, 344, and 422), eight in the context of non-transplant-related iatrogenic immunosuppression (cases SH2015-18, 106, 88, 153, 206, 252, 325, and 481), and three solid organ transplant recipients (cases SH2015-169, 335, and 501). Last, one unique case submitted by Dr Krishna (case SH2015-178) arose in the previously unreported context of congenital immune suppression, in a 16-year-old male patient with CHARGE syndrome (coloboma, heart defect, atresia of the nasal choanae, retardation of growth, genital and ear abnormalities, and deafness). MCU, EBV+ most likely arose in a background of age-related immune senescence in the first of these groups, with the median age of the patients being 74 years (range, 49-79 years). As with cases reported in the literature, iatrogenically immunosuppressed patients with connective tissue disorders were most commonly receiving methotrexate at the time of diagnosis (n = 4). Other drugs included azathioprine, mycophenolate mofetil, and imatinib. Six cases involved the oral cavity, four included the skin (two on the face, one each arm and leg), and seven arose at various sites in the gastrointestinal tract, including stomach (n = 2), small intestine (n = 3), sigmoid colon (n = 1), and anus (n = 1). Quantification of peripheral blood DNA was undertaken in five patients (cases SH2015-1, 106, 153, 335, and 501), encompassing age-related, iatrogenic immunosuppression, and posttransplant settings. The result was negative in all cases.

Characteristic pathologic features, including the spectrum of morphologies that may be encountered, were well illustrated by certain cases **Image 3**. Low-power view of cases SH2015-72 (Dr Dhesi) and SH2015-169 (Dr Nicolae) highlight the circumscribed nature of MCU, EBV+ and the presence of a confining band of small T cells at the base of the lesion. The case of Dr Dhesi was also an example of MCU, EBV+ with relatively few immunoblast and Reed-Sternberg–like cells, and it contrasted with that of Dr Grogg (SH2015-206), in which immunoblasts formed confluent sheets reminiscent of

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Table 3
Clinicopathologic Features of Mucocutaneous Ulcer, EBV+ Submitted to the Workshop

Case No.	Sex/Age, y	IS	Site	Treatment	Follow-up	Outcome, mo
SH2015-1	49/F	None	Oral mucosa	Rituximab	Relapse/remitting	Unknown
SH2015-72	77/F	None	Oral mucosa	Unknown	Unknown	Unknown
SH2015-299	79/M	None	Colon	Biopsy	Persistent	ANED, 12
SH2015-344	74/F	None	Nosal mucosa	Excision	CR	ANED, 48
SH2015-422	65/F	None	Stomach	Unknown	Unknown	Unknown
SH2015-18	67/M	A/I	Intestine	RIS	CR	ANED, 36
SH2015-88	58/F	A/I	Skin (right arm)	Rituximab, RIS	CR	Relapse
SH2015-106	77/M	A/I	Palate	RIS	CR	Unknown
SH2015-153	64/M	A/I	Anus	Rituximab, RIS	CR	ANED, 72
SH2015-206	49/F	A/I	Skin, oral mucosa	Excision, RIS	CR	Unknown
SH2015-252	17/F	A/I	Oral mucosa	Unknown	Unknown	Unknown
SH2015-325	81/M	A/I	Oral mucosa	R-CHOP (×1), R, RIS	CR	ANED
SH2015-481	63/F	A/I	Skin (lip)	Unknown	Unknown	Unknown
SH2015-169	57/M	PT	Small intestine	Unknown	Unknown	Unknown
SH2015-335	68/M	PT	Stomach	RIS	CR	ANED, 10
SH2015-501	32/M	PT	Small intestine	Rituximab, RIS	CR	ANED, 60
SH2015-178	16/M	PID	Nasopharyngeal mucosa; LN	Chemotherapy and HSCT	CR	Relapse, DOD

A/I, autoimmune or iatrogenic immunosuppression; ANED, alive no evidence of disease; CR, complete remission; DOD, died of disease; EBV, Epstein-Barr virus; HSCT, hematopoietic stem cell transplant; IS, form of immunosuppression or background; LN, lymph node; PID, primary immunodeficiency; PT, posttransplant; R, rituximab; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; RIS, reduction in immunosuppression.

DLBCL. The case submitted by Dr Roden (SH2015-344) was a good example of MCU, EBV+ mimicking CHL, and an angiocentric and angiodestructive growth pattern was evident in some, best illustrated in case SH2015-153 (Dr Quintanilla-Fend). Two of five cases tested demonstrated clonal immunoglobulin gene rearrangement. Only two were examined for T-cell receptor rearrangement, and neither showed evidence of a clone. In most cases with available clinical information, the lesions resolved spontaneously or on reduction in immunosuppression, with or without the addition of rituximab. One case relapsed but resolved following reduction in immunosuppression plus rituximab (SH2015-88), and one case (SH2015-1) ran a relapsing and remitting course despite receiving rituximab but without progression.

Large B-Cell Proliferations Associated With Chronic Inflammation (DLBCL Associated With Chronic Inflammation)

In the WHO classification, DLBCL associated with chronic inflammation (DLBCL-CI) is defined as a lymphoid neoplasm occurring in the context of longstanding chronic inflammation, showing an association with EBV.[45] This entity emerged from descriptions of large B-cell lymphoma presenting in the pleural cavities of patients with longstanding pyothorax, the latter usually a consequence of therapeutically induced pneumothorax as a treatment for tuberculosis.[46-51] Originally labeled as pyothorax-associated lymphoma (PAL), initial descriptions were in Japanese patients, but similar cases were subsequently reported in Western populations.[52-54] In the largest study to date, there was a mean latency period of 37 years (range, 20-60 years) between induced pneumothorax and diagnosis of PAL.[48] There is a striking male predominance despite chronic pyothorax being equally as prevalent in females, suggesting an increased susceptibility in men. Patients typically have pain, fever, respiratory symptoms, and a mass lesion in the pleural cavity.[48,52] The pathology is that of DLBCL, typically with immunoblastic or plasmablastic morphology and a post–germinal center phenotype. Most cases are positive for EBV, usually with a type III latency pattern, and aberrant expression of T-cell antigens is not infrequent.[47,48,52,55] Most cases are localized at presentation but despite this, and irrespective of treatment modality, run an aggressive clinical course with median survivals of less than 1 year and a 5-year overall survival of around 20% quoted.[48,52]

The concept of EBV-associated DLBCL arising on a background of chronic suppurative inflammation was subsequently extended to include cases arising in association with chronic osteomyelitis, venous ulcers, and metallic joint prostheses and surgical mesh implants.[56-58] As with PAL, these cases displayed a long latency period between the onset of inflammation and development of lymphoma and a marked male predominance, although the case numbers are too few to comment on treatment and outcome. Nevertheless, such cases are included under the more generic name of DLBCL associated with chronic inflammation currently employed in the WHO classification.[45]

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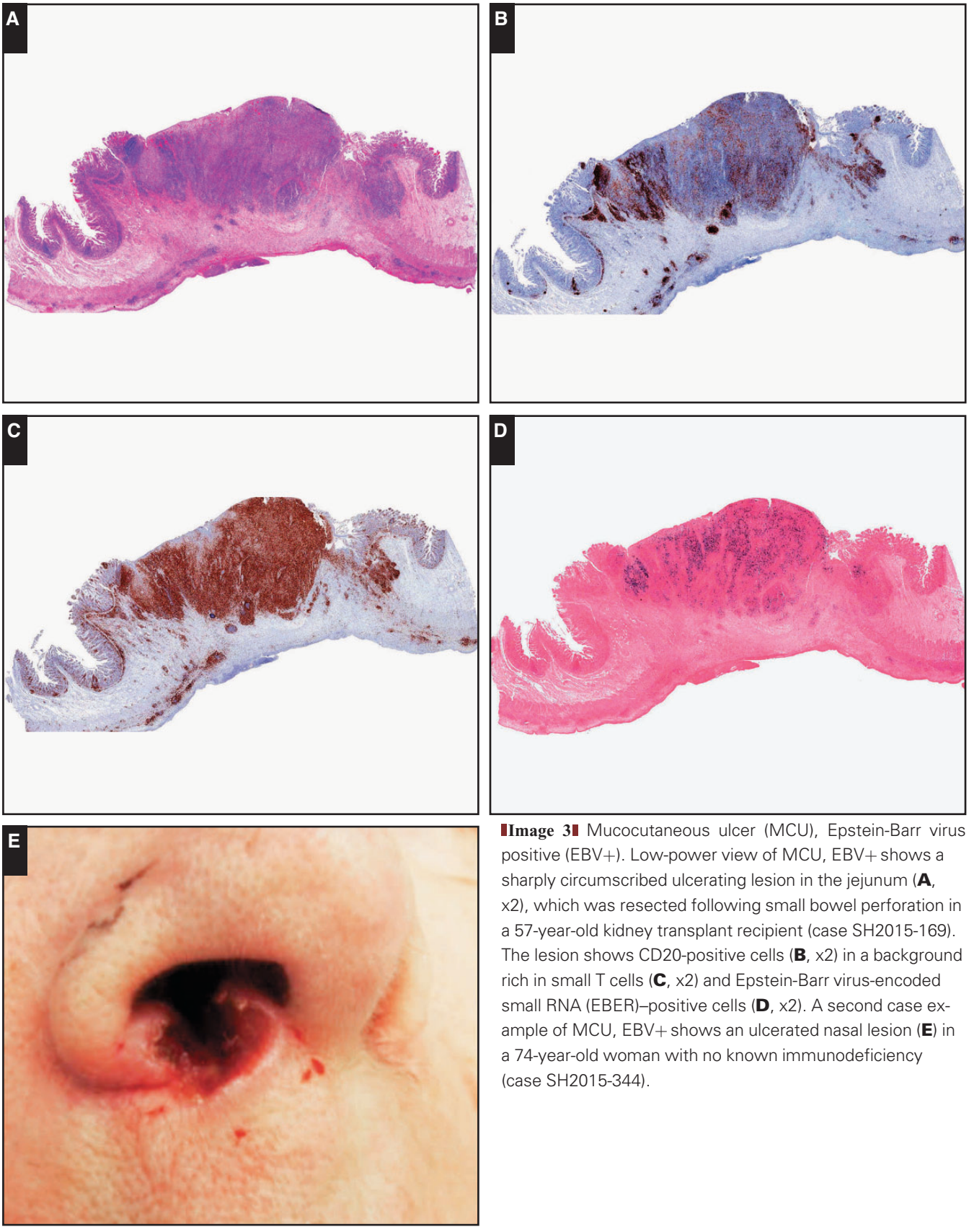

Image 3 Mucocutaneous ulcer (MCU), Epstein-Barr virus positive (EBV+). Low-power view of MCU, EBV+ shows a sharply circumscribed ulcerating lesion in the jejunum (**A**, x2), which was resected following small bowel perforation in a 57-year-old kidney transplant recipient (case SH2015-169). The lesion shows CD20-positive cells (**B**, x2) in a background rich in small T cells (**C**, x2) and Epstein-Barr virus-encoded small RNA (EBER)–positive cells (**D**, x2). A second case example of MCU, EBV+ shows an ulcerated nasal lesion (**E**) in a 74-year-old woman with no known immunodeficiency (case SH2015-344).

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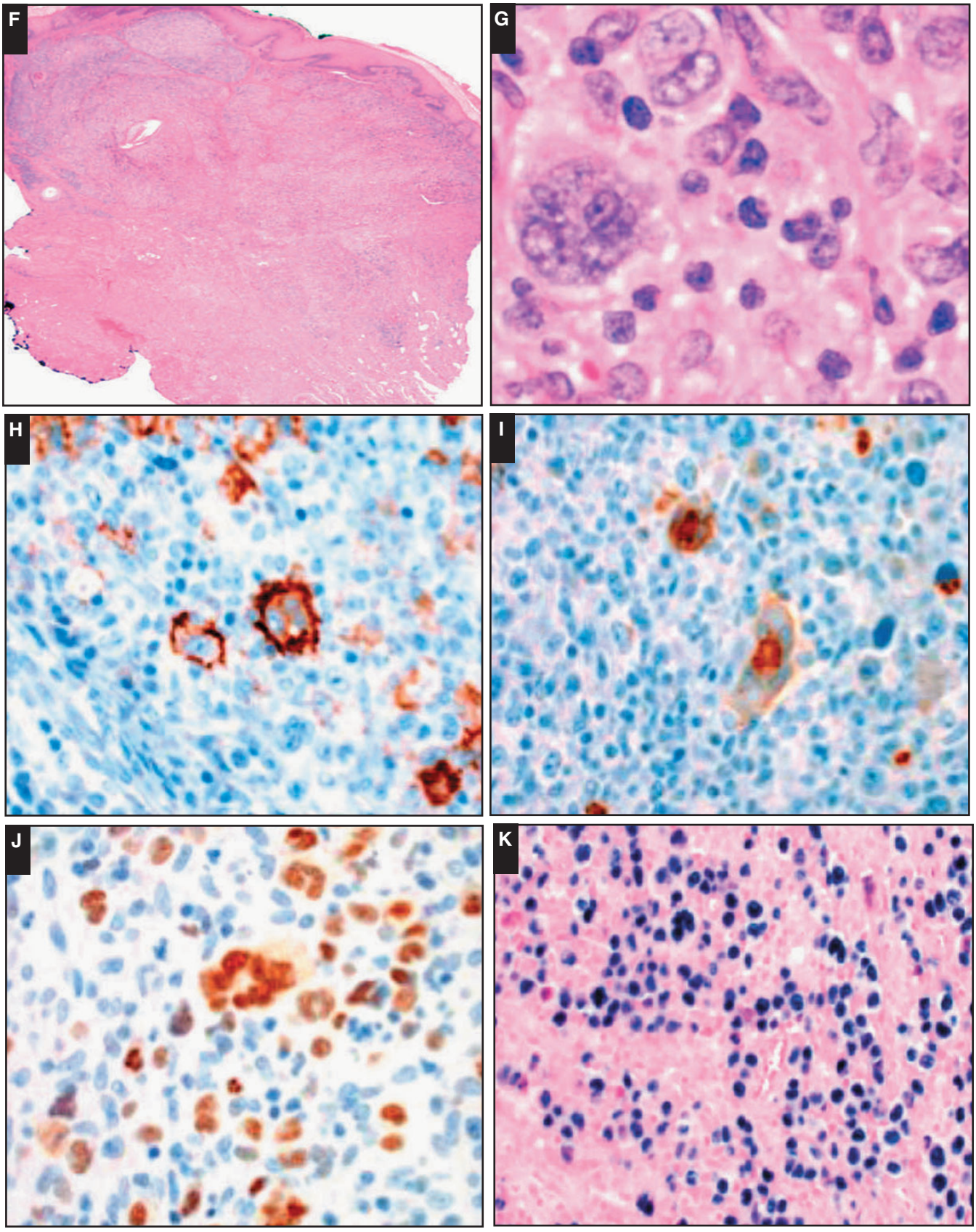

Image 3 (cont) H&E images show a shallow, well-circumscribed lymphoid proliferation (**F**, x2) with atypical large cells in a mixed background, mimicking classical Hodgkin lymphoma (**G**, x40). Immunohistochemistry is positive for CD30 (**H**, x40), CD15 (**I**, x40), and OCT2 (**J**, x40) in the atypical large cells, whereas in situ hybridization for EBER is positive in a range of small to large cells (**K**, x40).

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More recently, a group of neoplasms has been described that shares some features with previously documented cases of DLBCL-CI and is sometimes appended this moniker but differs in several respects. All constitute stage IE EBV-positive large B-cell proliferations that appear to arise in confined spaces in association with fibrin, either in the form of thrombus or in cystic lesions showing evidence of previous hemorrhage with organization. The initial cases were reported as incidental findings in the cardiovascular system in association with aortic grafts, atrial thrombus, atrial myxoma, or replacement heart valves.[59-64] Other cases have been described in the inner linings of cystic lesions, including splenic pseudocyst, renal cyst, adrenal pseudocyst, hydrocele, testicular pseudocyst, and cystic ovarian teratoma.[65-68] No mass lesion is found. Instead, microscopic aggregates of large B cells are seen lying within thrombus or in amorphous fibrinous material showing signs of previous hemorrhage, the latter lining cyst walls or lying close to the surface of atrial myxoma.[59-68] The large B-cell proliferations are clonal, typically have a post–germinal center phenotype, and are almost always EBV positive. A type III latency pattern is most frequently seen.[59,65] In contrast to PAL, as well as the absence of a mass lesion, no suppurative inflammation is seen and the outcome appears to be excellent. All the reported cases with follow-up were either alive with no evidence of disease or were in complete remission when they died of unrelated causes.[59-68] Although many of the patients were treated with adriamycin-containing regimens, some were managed to equally good effect with surgery alone or single-agent rituximab, suggesting that aggressive chemotherapy may represent overtreatment.[60,64-66]

These differences have led some authors to propose that these lymphoproliferations should be regarded separately from the prototypic DLBCL-CI, PAL and alternative names have been suggested to emphasize their more indolent behavior and unique pathologic features. These include fibrin-associated large B-cell lymphoma, microscopic DLBCL, and cystic DLBCL.[59,66,68] However, a solitary report of a case involving a subdural hematoma with an invasive lymphoma in the adjacent brain questions the assumption that benign behavior is guaranteed, although there is no clear documentation of progression of an initial microscopic lymphoma to the invasive component.[69] This, coupled with the small number of cases studied to date, makes it difficult to draw definite conclusions as to the relatively benign behavior of these lesions. Therefore, it is likely that they will be retained in the category of DLBCL-CI in the upcoming revision of the WHO classification but separated under the heading "incidental DLBCL associated with chronic inflammation." The Workshop Review Panel, however, preferred the term *large B-cell proliferations associated with chronic inflammation* (LBP-CI), in recognition of the variable clinical course exhibited by these lesions.

The pathogenetic mechanisms of large B-cell proliferations associated with chronic inflammation are not fully elucidated, but there is evidence to suggest that in pyothorax-associated lymphomas, as well as the more indolent group of lymphoproliferations, longstanding inflammation in an enclosed space results in accumulation of cytokines such as interleukin (IL)–6 and IL-10. The former is thought to enhance the growth of EBV-infected B cells that have escaped host immune surveillance as a consequence of the latter.[70,71]

The differential diagnosis of LBP-CI includes EBV-positive DLBCL (of the elderly), with which it shares many features, including a post–germinal center phenotype, a type III latency pattern, and a propensity to occur in the elderly.[72,73] However, LBP-CI is localized at presentation and associated with an underlying lesion of long standing, be it chronic pyothorax, atrial myxoma, mural thrombus, or cyst. DLBCL-CI arising in the pleural cavity differs from primary effusion lymphoma (PEL) in lacking HHV8 and a history of immune suppression.[74] Also, cases conforming to descriptions of PAL have mass lesions, which is not the case for PEL. Lymphomatoid granulomatosis differs from DLBCL-CI in showing multifocal involvement of lung parenchyma in most cases, together with numerous background small T cells.[75]

Five cases were submitted to the workshop under the heading of DLBCL-CI (SH2015-68, 147, 176, 470, and 471). There were no cases of PAL, with all five conforming to the pattern of LBP-CI described above. Two cases were associated with atrial myxoma, two had mural thrombus (one intra-atrial and one within an aortic aneurysm), and one case arose within a renal cyst. The cases of Dr Graces (SH2015-68) and Dr Ruano (SH2015-470 and SH2015-471) illustrate this spectrum of presentation and the characteristic pathologic features **Image 4**. As with similar cases reported in the literature, these lymphoproliferations comprised microscopic collections of EBV-positive large B cells with a post–germinal center phenotype and usually a type III latency pattern. The clinicopathologic features are summarized in **Table 4** along with details of previously reported cases. They are localized non-mass-forming lesions that typically do not progress. Two cases with follow-up were treated with R-CHOP and had long-term remission. However, as illustrated in SH2015-147 submitted by Dr Rogeny, although excision alone may result in complete remission, local recurrence remains a possibility. In addition, the associated thrombus in this case seems to have been partly or wholly responsible for the patient's demise.

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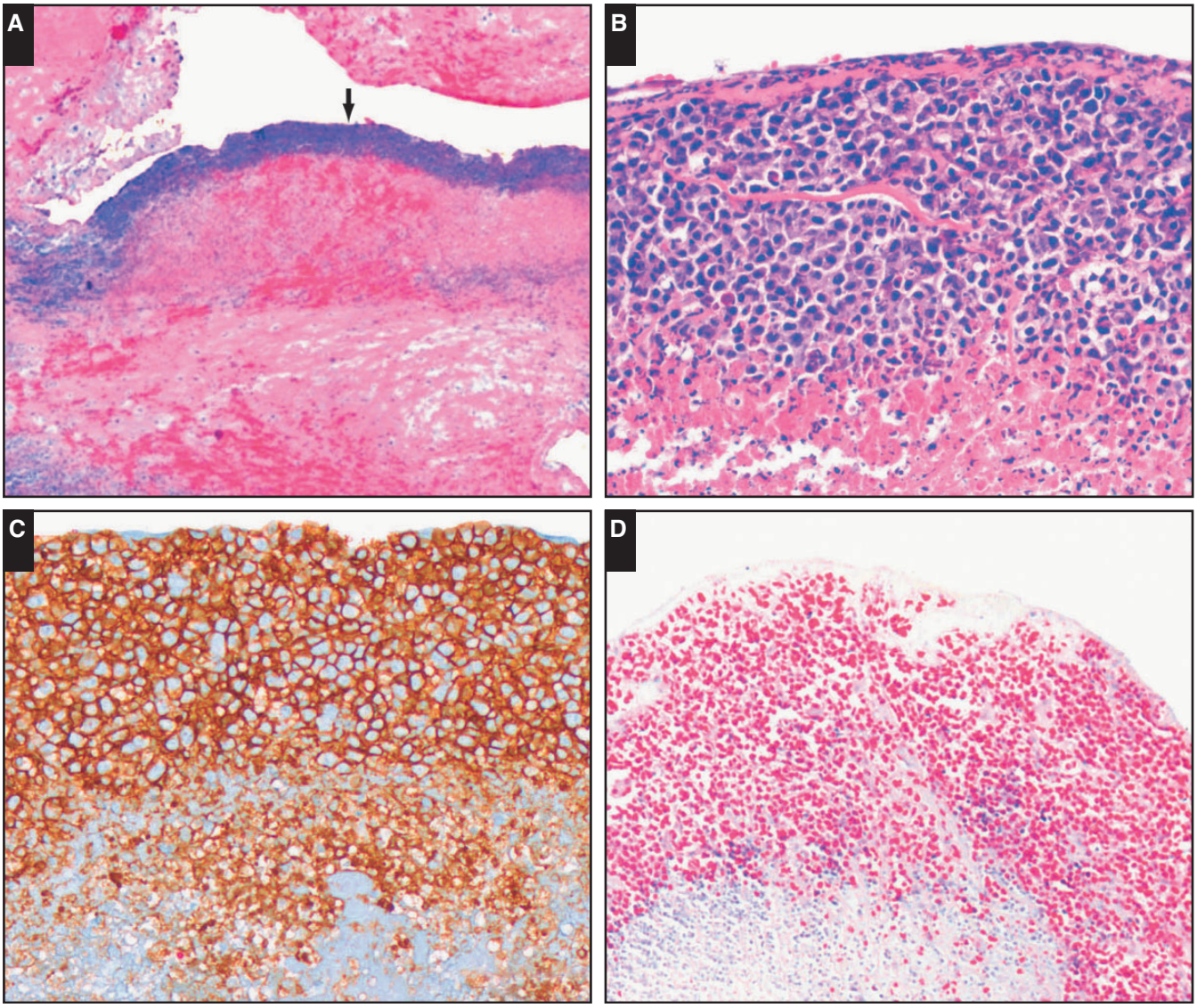

Image 4 Large B-cell proliferations associated with chronic inflammation. Three case examples are illustrated, all of which occurred in immunocompetent patients. A left atrial myxoma in a 50-year-old otherwise healthy man (case SH2015-68) shows a gelatinous mass with a rim of highly pleomorphic large lymphoid cells (arrow) (**A**, x4; **B**, x40), expressing CD20 (**C**, x40), and Epstein-Barr virus–encoded small RNA in a subset of cells (**D**, x40).

Conclusions

The cases submitted to the workshop clearly demonstrated that EBV-positive proliferations of varied malignant potential, as defined in the introduction to this section, may occur in a variety of different settings associated with an altered immune state. Thus, cases categorized as hyperplasias; polymorphic LPDs; MCU, EBV+; and LBP-CI were encountered in posttransplant patients, as well as in association with iatrogenic immune suppression (usually in patients with autoimmune disease), congenital immune deficiency and HIV infection, and as a presumed consequence of immune senescence in elderly individuals. Moreover, in many instances, the biology of morphologically similar proliferations appeared to be similar, irrespective of the clinical scenario in which they were encountered, the latter being most important in dictating how best to therapeutically restore immunity to as near normal as possible. Although more study is required to determine if this is truly the case, some general comments of practical use can be made. For hyperplasias and polymorphic LPDs, a graded approach to treatment is recommended, ranging from observation, to reduction in immunosuppression (reduced dose of immunosuppressive agents or introduction of HAART in HIV), to single-agent

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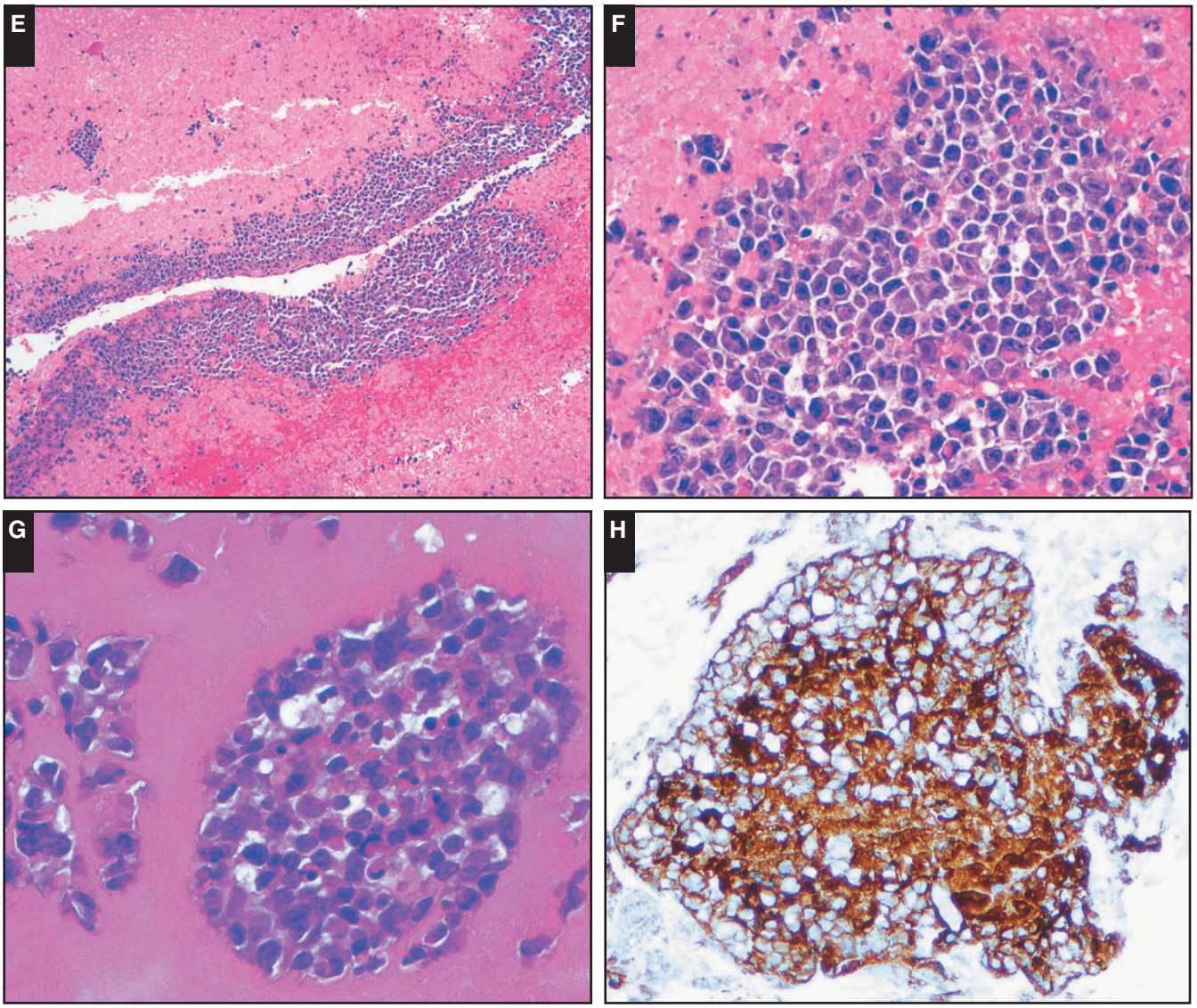

Image 4 (cont) Friable pieces of thrombus from an aneurysm repair of the descending aorta in a 56-year-old man show clusters of pleomorphic cells with brisk mitotic activity (case SH2015-176, **E**, x10; and **F**, x40). An example of a pedunculated fossa ovalis mass showing pleomorphic large clusters of CD20-positive cells associated with fibrin (case SH2015-470, **G** and **H**, x40).

rituximab, to rituximab plus multiagent chemotherapy. The initial starting point on this scale of treatment is determined by a number of factors, including the pathologic findings (eg, most cases of hyperplasia spontaneously resolve), the practicality of reducing immunosuppression (eg, balancing the risk to a transplanted organ with the risk of progression to an aggressive lymphoproliferation), and the clinical extent and apparent aggressiveness of the disease at presentation.

For MCU, EBV+, a similar approach is advocated, with the caveat that aggressive chemotherapy is not required; most cases spontaneously resolve or complete remission occurs as a consequence of reduction in immunosuppression, with single-agent rituximab being reserved for particularly recalcitrant lesions. Management of DLBCL-CI is more difficult to advise upon. No cases of PAL were submitted to the workshop, and it is likely that few examples of this aggressive lymphoma will be encountered in the future due to the altered management of tuberculosis. Thus, many cases will fall into the category we prefer to call LBP-CI and which the 2016 WHO update proposes to name "incidental DLBCL associated with chronic inflammation." While it is quite possible that R-CHOP may represent overly aggressive treatment for such lesions, there is currently insufficient evidence on the efficacy of alternative approaches to draw meaningful conclusions. However, if

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Table 4
Clinicopathologic Features of Large B-cell Proliferations Associated With Chronic Inflammation in the Literature and Submitted to the Workshop

Reference/ Case No.	Sex/Age, y	Site	Phenotype	Clonality by PCR	EBER	LMP1	EBNA2	BZLF1	Treatment	Outcome, mo
Gruver et al[59]	55/M	Aortic root graft	Post-GC	MC	+	+	+	ND	R-CEOP	ANED, 16
	56/M	Atrial thrombus	GC	MC	+	+	+	ND	R-CHOP	ANED, 8
	75/M	Myxomatous mitral valve thrombus	GC	MC	–	–	–	ND	R-CHOP	ANED, 39
Loong et al[65]	29/M	Splenic wall cyst	Post-GC	MC	+	+	+	ND	Rituximab	ANED, 6
	88/M	Hydrocele	Post-GC*	MC	+	+	+	ND	Unknown	Unknown
	70/F	Atrial myxoma	Post-GC	MC	+	+	+	ND	R-CEOP	DOU, 5
	78/M	Prosthetic knee	Post-GC	MC	+	+	+	ND	XRT	ANED, 84
Aguilar et al[60]	52/M	Atrial myxoma	Post-GC	MC	+	+	+	ND	Excision	ANED, 42
Quigley et al[61]	29/M	Atrial thrombus	Unknown	MC	+	ND	ND	ND	CHOP	ANED, 24
Miller et al[64]	48/M	Aortic graft	Post-GC	MC	+	ND	ND	ND	None	Died postoperatively
	80/F	Bovine heart valve	Post-GC	MC	+	ND	ND	ND	Treated for breast cancer	DOU
	79/F	Aortic graft	Post-GC	MC	+	ND	ND	ND	Excision	ANED, 6
Boroumand et al[66]	63/F	Adrenal pseudocyst	Post-GC	ND	+	–	ND	ND	R-CHOP + XRT	ANED, 40
	27/M	Testicular pseudocyst	Post-GC	ND	+	+	ND	ND	Excision	ANED, 9
Valli et al[67]	46/M	Renal cyst	Post-GC	ND	+	ND	ND	ND	R-CHOP	Current case
Valli et al[68]	56/F	Cystic ovarian teratoma	Post-GC	MC	+	ND	ND	ND	R-COMP	ANED, 8
Svec et al[62]	60/F	Cardiac myxoma	Post-GC	ND	+	+	+	ND	R-CHOP	ANED, 7
Bagwan et al[63]	50/M	Aortic valve thrombus	GC	ND	ND	–	ND	ND	R-CHOP	Died ruptured valve, 6; NED at autopsy
	81/F	Atrial myxoma	GC	ND	ND	ND	ND	ND	R-CHOP	Current case
SH2015-68	50/M	Atrial myxoma	Post-GC	ND	+	+	+	+	Unknown	Lost to FU
SH2015-147	54/M	Atrial myxoma	Post-GC	ND; κ restricted		+	+	–	Excision	Relapse, 24; no further treatment; died of embolic disease
SH2015-176	56/M	Aortic aneurysm thrombus	Post-GC	MC	+	+	+	+/–	Excision	Persisted without progression, then R-CHOP; no further FU
SH2015-470	56/M	Atrial thrombus	Post-GC	MC	+	–	ND	+/–	R-CHOP	ANED, 46
SH2015-471	61/M	Renal cyst	Post-GC	ND	+	–	ND	–	R-CHOP	ANED, 51

ANED, alive no evidence of disease; BZLF1, Epstein-Barr virus (EBV) basic leucine zipper family 1; CHOP, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; DOU, died of unrelated cause; EBER, EBV-encoded small RNA; EBNA2, EBV nuclear antigen 2; FU, follow-up; GC, germinal center; LMP1, latent membrane protein 1; MC, monoclonal; ND, not done; NED, no evidence of disease; PCR, polymerase chain reaction; R-CEOP, rituximab, cyclophosphamide, etoposide, vincristine, prednisone; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone; R-COMP, rituximab, cyclophosphamide, nonpegylated liposomal doxorubicin, vincristine, prednisone; XRT, radiotherapy; +, positive; –, negative.

R-CHOP is given, the outcome is likely to be excellent provided no mass lesion is present at diagnosis.

Given the spectrum of treatment options available, recognition and accurate diagnosis of these entities is essential. For hyperplasias and polymorphic LPDs, appropriate management at an early stage is important in view of the albeit low risk of progression to a more aggressive neoplasm, while it is essential to differentiate MCU, EBV+ and LBP-CI from more aggressive mimics in view of prognostic and, at least for the former, therapeutic considerations. An awareness of the characteristic features as well as the spectrum of morphologies associated with these various disorders, as discussed in the preceding sections, is obviously paramount in accurate diagnosis. In addition, the importance of clinical information, particularly current and prior drug history, and correlation with the pathologic features cannot be overemphasized. A concise summary of EBV+ B-cell proliferations of varied malignant potential can be found in **Table 5**.

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Table 5
Summary Table: EBV-Associated B-Cell Proliferations of Varied Malignant Potential

B-cell hyperplasias (nondestructive lesions)
Mass-forming lesions with preservation of tissue architecture
EBER expression variable in follicles or in interfollicular areas; typically localized to one or more hyperplastic follicles in follicular hyperplasia
Require EBV positivity for diagnosis, especially for follicular and plasmacytic hyperplasia
Small clonal rearrangements or simple karyotypic abnormalities may be present
Clinical correlation essential not to overdiagnose or overtreat
Most cases regress spontaneously or with reduction of immunosuppression
Surgical excision often sufficient management for obstructive masses in children
Rarely associated with subsequent development of more aggressive immunodeficiency-related lymphoproliferative disorders
Most cases regress spontaneously or with reduction of immunosuppression
Polymorphic B-lymphoproliferative disorders
Efface architecture or cause destructive masses
Polymorphous infiltrate with full spectrum of B-cell maturation stages and abundant immunoblasts, sometimes with Hodgkin-Reed-Sternberg–like cells
Important to separate from classical Hodgkin lymphoma, EBV+ mucocutaneous ulcer, and T-cell/histiocyte-rich large B-cell lymphoma
Almost all show clonal IG gene rearrangements
Simple karyotypes may be present
Most cases respond to reduction or withdrawal of immunosuppression or initiation of HAART in patients with HIV, but some may require aggressive treatment
EBV+ mucocutaneous ulcer
Well-circumscribed, often painful, ulcerating lesions arising at mucosal or cutaneous sites without mass lesions
Polymorphous infiltrate with admixed small lymphocytes, plasma cells, histiocytes, and eosinophils; immunoblasts and Hodgkin-Reed-Sternberg–like cells may be numerous and mimic classical Hodgkin lymphoma
Rim of small T cells in base of ulcer
Clonal IG or T-cell receptor gene rearrangements detected in half of cases
Most cases regress spontaneously or with reduction of immunosuppression; rare cases may exhibit a relapsing and remitting course without progression
Large B-cell proliferations associated with chronic inflammation
EBV-driven clonal large B-cell proliferations in a localized microenvironment associated with inflammation and chronic immune stimulation
Typically occur in immunocompetent patients
Subset of cases associated with fibrin thrombi, joint prosthesis, and atrial myxoma, and cysts display indolent growth; seldom disseminate (large B-cell proliferations associated with chronic inflammation/"incidental DLBCL associated with chronic inflammation")
Differ from pyothorax-associated lymphoma as they are noninvasive and do not form mass lesions
"DLBCL" name may cause unnecessary overtreatment

DLBCL, diffuse large B-cell lymphoma; EBER, EBV-encoded small RNA; EBV, Epstein-Barr virus; IG, immunoglobulin; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

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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/2loeRGX. 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).

References

1. Swerdlow SH, Weber SA, Chadburn A, et al. Post-transplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC; 2008:343-349.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
3. Meru N, Davison S, Whitehead L, et al. Epstein-Barr virus infection in paediatric liver transplant recipients: detection of the virus in post-transplant tonsillectomy specimens. *Mol Pathol*. 2001;54:264-269.
4. Harris NL, Swerdlow SH, Frizzera G, et al. *Post-Transplant Lymphoproliferative Disorders*. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Lyon, France: IARC; 2001:264-269.
5. Williamson RA, Huang RY, Shapiro NL. Adenotonsillar histopathology after organ transplantation. *Otolaryngology Head Neck Surg*. 2001;125:231-240.
6. Shapiro NL, Strocker AM, Bhattacharyya N. Risk factors for adenotonsillar hypertrophy in children following solid organ transplantation. *Int J Pediatric Otorhinolaryngol*. 2003;67:151-155.
7. Nalesnik MA, Jaffe R, Starzl TE, et al. The pathology of post-transplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. *Am J Pathol*. 1988;133:173-192.
8. Cesarman E, Chadburn A, Liu YF, et al. BCL-6 gene mutations in posttransplantation lymphoproliferative disorders predict response to therapy and clinical outcome. *Blood* 1998;92:2294-2302.
9. Delecluse HJ, Rouault JP, Jeammot B, et al. Bcl6/Laz3 rearrangements in post-transplant lymphoproliferative disorders. *Br J Haematol*. 1995;91:101-103.
10. Cerri M, Capello D, Muti G, et al. Aberrant somatic hypermutation in post-transplant lymphoproliferative disorders. *Br J Haematol*. 2004;127:362-364.

DOI: 10.1093/ajcp/aqw214

11. Poirel HA, Bernheim A, Schneider A, et al. Characteristic pattern of chromosomal imbalances in posttransplantation lymphoproliferative disorders: correlation with histopathological subcategories and EBV status. *Transplantation*. 2005;80:176-184.
12. Djokic M, Le Beau MM, Swinnen LJ, et al. Post-transplant lymphoproliferative disorder subtypes correlate with different recurring chromosomal abnormalities. *Genes Chromosomes Cancer*. 2006;45:313-318.
13. Vakiani E, Nandula SV, Subramaniyam S, et al. Cytogenetic analysis of B-cell posttransplant lymphoproliferations validates the World Health Organization classification and suggests inclusion of florid follicular hyperplasia as a precursor lesion. *Hum Pathol*. 2007;38:315-325.
14. Vakiani E, Basso K, Klein U, et al. Genetic and phenotypic analysis of B-cell post-transplant lymphoproliferative disorders provides insights into disease biology. *Hematol Oncol*. 2008;26:199-211.
15. Lones MA, Mishalani S, Shintaku IP, et al. Changes in tonsils and adenoids in children with posttransplant lymphoproliferative disorder: report of three cases with early involvement of Waldeyer's ring. *Hum Pathol*. 1995;26:525-530.
16. Sevilla DW, Murty VV, Sun XL, et al. Cytogenetic abnormalities in reactive lymphoid hyperplasia: byproducts of the germinal centre reaction or indicators of lymphoma? *Hematol Oncol*. 2011;29:81-90.
17. Roux C, Nicolini FE, Rea D, et al. Reversible lymph node follicular hyperplasia associated with dasatinib treatment of chronic myeloid leukemia in chronic phase. *Blood*. 2013;122:3082-3084.
18. Ozawa MG, Ewalt MD, Gratzinger D. Dasatinib-related follicular hyperplasia: an underrecognized entity with characteristic morphology. *Am J Surg Pathol*. 2015;39:1363-1369.
19. Wu TT, Swerdlow SH, Locker J, et al. Recurrent Epstein-Barr virus–associated lesions in organ transplant recipients. *Hum Pathol*. 1996;27:157-164.
20. Knowles DM, Cesarman E, Chadburn A, et al. Correlative morphologic and molecular genetic analysis demonstrates three distinct categories of posttransplantation lymphoproliferative disorders. *Blood*. 1995;85:552-565.
21. Dojcinov SD, Venkataraman G, Pittaluga S, et al. Age-related EBV-associated lymphoproliferative disorders in the Western population: a spectrum of reactive lymphoid hyperplasia and lymphoma. *Blood*. 2011;117:4726-4735.
22. Capello D, Rossi D, Gaidano G. Post-transplant lymphoproliferative disorders: molecular basis of disease histogenesis and pathogenesis. *Hematol Oncol*. 2005;23:61-67.
23. Webber SA, Naftel DC, Fricker FJ, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. *Lancet*. 2006;367:233-239.
24. Kamel OW. Iatrogenic lymphoproliferative disorders in nontransplantation settings. *Semin Diagn Pathol*. 1997;14:27-34.
25. Kamel OW, Weiss LM, van de Rijn M, et al. Hodgkin's disease and lymphoproliferations resembling Hodgkin's disease in patients receiving long-term low-dose methotrexate therapy. *Am J Surg Pathol*. 1996;20:1279-1287.
26. Hasserjian RP, Chen S, Perkins SL, et al. Immunomodulator agent-related lymphoproliferative disorders. *Mod Pathol*. 2009;22:1532-1540.
27. Wolfe F, Michaud K. The effect of methotrexate and anti–tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation, *arthritis and Rheumatism*. 2007;56:1433-1439.
28. Rizzi R, Curci P, Delia M, et al. Spontaneous remission of "methotrexate-associated lymphoproliferative disorders" after discontinuation of immunosuppressive treatment for autoimmune disease: review of the literature. *Med Oncol*. 2009;26:1-9.
29. Wong AK, Kerkoutian S, Said J, et al. Risk of lymphoma in patients receiving antitumor necrosis factor therapy: a meta-analysis of published randomized controlled studies. *Clin Rheumatol*. 2012;31:631-636.
30. Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression. *Eur J Haematol*. 2013;91:20-28.
31. Buxton J, Leen C, Goodlad JR. Polymorphic lymphoid proliferations occurring in HIV-positive patients: report of a case responding to HAART. *Virchows Arch*. 2012;461:93-98.
32. Dojcinov SD, Venkataraman G, Raffeld M, et al. EBV positive mucocutaneous ulcer—a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol*. 2010;34:405-417.
33. Curry JL, Prieto VG, Jones DM, et al. Transient iatrogenic immunodeficiency-related B-cell lymphoproliferative disorder of the skin in a patient with mycosis fungoides/Sezary syndrome. *J Cutan Pathol*. 2011;38:295-297.
34. Au WY, Ma ES, Choy C, et al. Therapy-related lymphomas in patients with autoimmune diseases after treatment with disease-modifying anti-rheumatic drugs. *Am J Hematol*. 2006;81:5-11.
35. Kalantzis A, Marshman Z, Falconer DT, et al. Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontics*. 2005;100:52-62.
36. McGinness JL, Spicknall KE, Mutasim DF. Azathioprine-induced EBV-positive mucocutaneous ulcer. *J Cutan Pathol*. 2012;39:377-381.
37. Yamakawa N, Fujimoto M, Kawabata D, et al. A clinical, pathological, and genetic characterization of methotrexate-associated lymphoproliferative disorders. *J Rheumatol*. 2014;41:293-299.
38. Hart M, Thakral B, Yohe S, et al. EBV-positive mucocutaneous ulcer in organ transplant recipients: a localized indolent posttransplant lymphoproliferative disorder. *Am J Surg Pathol*. 2014;38:1522-1529.
39. Attard AA, Praveen P, Dunn PJ, et al. Epstein-Barr virus-positive mucocutaneous ulcer of the oral cavity: the importance of having a detailed clinical history to reach a correct diagnosis. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012;114:e37-e39.
40. Sadasivam N, Johnson RJ, Owen RG. Resolution of methotrexate-induced Epstein-Barr virus–associated mucocutaneous ulcer. *Br J Haematol*. 2014;165:584.
41. Cohen JI, Kimura H, Nakamura S, et al. Epstein-Barr virus–associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8-9 September 2008. *Ann Oncol*. 2009;20:1472-1482.
42. Callan MF, Steven N, Krausa P, et al. Large clonal expansions of CD8+ T cells in acute infectious mononucleosis. *Nat Med*. 1996;2:906-911.

DOI: 10.1093/ajcp/aqw214

43. Bharadwaj M, Burrows SR, Burrows JM, et al. Longitudinal dynamics of antigen-specific CD8+ cytotoxic T lymphocytes following primary Epstein-Barr virus infection. *Blood*. 2001;98:2588-2589.
44. Tanaka A, Shigematsu H, Kojima M, et al. Methotrexate-associated lymphoproliferative disorder arising in a patient with adult Still's disease. *J Oral Maxillofac Surg*. 2008;66:1492-1495.
45. Chan JKC, Aozasa K, Gaulard P. *DLBCL Associated With Chronic Inflammation*. In: Swerdlow SH, Campo E, Harris NL, eds. Lyon, France: IARC; 2008:245-246.
46. Aozasa K, Takakuwa T, Nakatsuka S. Pyothorax-associated lymphoma: a lymphoma developing in chronic inflammation. *Adv Anat Pathol*. 2005;12:324-331.
47. Yamato H, Ohshima K, Suzumiya J, et al. Evidence for local immunosuppression and demonstration of c-myc amplification in pyothorax-associated lymphoma. *Histopathology*. 2001;39:163-171.
48. Nakatsuka S, Yao M, Hoshida Y, et al. Pyothorax-associated lymphoma: a review of 106 cases. *J Clin Oncol*. 2002;20:4255-4260.
49. Fukayama M, Ibuka T, Hayashi Y, et al. Epstein-Barr virus in pyothorax-associated pleural lymphoma. *Am J Pathol*. 1993;143:1044-1049.
50. Ohsawa M, Tomita Y, Kanno H, et al. Role of Epstein-Barr virus in pleural lymphomagenesis. *Mod Pathol*. 1995;8:848-853.
51. Kanno H, Yasunaga Y, Ohsawa M, et al. Expression of Epstein-Barr virus latent infection genes and oncogenes in lymphoma cell lines derived from pyothorax-associated lymphoma. *Int J Cancer*. 1996;67:86-94.
52. Petitjean B, Jardin F, Joly B, et al. Pyothorax-associated lymphoma: a peculiar clinicopathologic entity derived from B cells at late stage of differentiation and with occasional aberrant dual B- and T-cell phenotype. *Am J Surg Pathol*. 2002;26:724-732.
53. Ascani S, Piccioli M, Poggi S, et al. Pyothorax-associated lymphoma: description of the first two cases detected in Italy. *Ann Oncol*. 1997;8:1133-1138.
54. Androulaki A, Drakos E, Hatzianastassiou D, et al. Pyothorax-associated lymphoma (PAL): a Western case with marked angiocentricity and review of the literature. *Histopathology*. 2004;44:69-76.
55. Mori N, Yatabe Y, Narita M, et al. Pyothorax-associated lymphoma: an unusual case with biphenotypic character of T and B cells. *Am J Surg Pathol*. 1996;20:760-766.
56. Copie-Bergman C, Niedobitek G, Mangham DC, et al. Epstein-Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. *J Pathol*. 1997;183:287-292.
57. Cheuk W, Chan AC, Chan JK, et al. Metallic implant-associated lymphoma: a distinct subgroup of large B-cell lymphoma related to pyothorax-associated lymphoma? *Am J Surg Pathol*. 2005;29:832-836.
58. Fujimoto M, Haga H, Okamoto M, et al. EBV-associated diffuse large B-cell lymphoma arising in the chest wall with surgical mesh implant. *Pathol Int*. 2008;58:668-671.
59. Gruver AM, Huba MA, Dogan A, et al. Fibrin-associated large B-cell lymphoma: part of the spectrum of cardiac lymphomas. *Am J Surg Pathol*. 2012;36:1527-1537.
60. Aguilar C, Beltran B, Quinones P, et al. Large B-cell lymphoma arising in cardiac myxoma or intracardiac fibrinous mass: a localized lymphoma usually associated with Epstein-Barr virus? *Cardiovasc Pathol*. 2015;24:60-64.
61. Quigley MM, Schwartzman E, Boswell PD, et al. A unique atrial primary cardiac lymphoma mimicking myxoma presenting with embolic stroke: a case report. *Blood*. 2003;101:4708-4710.
62. Svec A, Rangaiah M, Giles M, et al. EBV+ diffuse large B-cell lymphoma arising within atrial myxoma: an example of a distinct primary cardiac EBV+ DLBCL of immunocompetent patients. *Pathol Res Pract*. 2012;208:172-176.
63. Bagwan IN, Desai S, Wotherspoon A, et al. Unusual presentation of primary cardiac lymphoma. *Interact Cardiovasc Thorac Surg*. 2009;9:127-129.
64. Miller DV, Firchau DJ, McClure RF, et al. Epstein-Barr virus–associated diffuse large B-cell lymphoma arising on cardiac prostheses. *Am J Surg Pathol*. 2010;34:377-384.
65. Loong F, Chan AC, Ho BC, et al. Diffuse large B-cell lymphoma associated with chronic inflammation as an incidental finding and new clinical scenarios. *Mod Pathol*. 2010;23:493-501.
66. Boroumand N, Ly TL, Sonstein J, et al. Microscopic diffuse large B-cell lymphoma (DLBCL) occurring in pseudocysts: do these tumors belong to the category of DLBCL associated with chronic inflammation? *Am J Surg Pathol*. 2012;36:1074-1080.
67. Valli R, Piana S, Capodanno I, et al. Diffuse large B-cell lymphoma associated with chronic inflammation arising in a renal pseudocyst. *Int J Surg Pathol*. 2011;19:117-119.
68. Valli R, Froio E, Alvarez de Celis MI, et al. Diffuse large B-cell lymphoma occurring in an ovarian cystic teratoma: expanding the spectrum of large B-cell lymphoma associated with chronic inflammation. *Hum Pathol*. 2014;45:2507-2511.
69. Kameda K, Shono T, Takagishi S, et al. Epstein-Barr virus–positive diffuse large B-cell primary central nervous system lymphoma associated with organized chronic subdural hematoma: a case report and review of the literature. *Pathol Int*. 2015;65:138-143.
70. Kanno H, Aozasa K. Mechanism for the development of pyothorax-associated lymphoma. *Pathol Int*. 1998;48:653-664.
71. Kanno H, Naka N, Yasunaga Y, et al. Production of the immunosuppressive cytokine interleukin-10 by Epstein-Barr-virus-expressing pyothorax-associated lymphoma: possible role in the development of overt lymphoma in immunocompetent hosts. *Am J Pathol*. 1997;150:349-357.
72. Oyama T, Ichimura K, Suzuki R, et al. Senile EBV+ B-cell lymphoproliferative disorders: a clinicopathologic study of 22 patients. *Am J Surg Pathol*. 2003;27:16-26.
73. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. *Clin Cancer Res*. 2007;13:5124-5132.
74. Said J, Cesarman E. *Primary Effusion Lymphoma*. In: Swerdlow SH, Campo E, Harris NL, eds. Lyon, France: IARC; 2008:260-261.
75. Katzenstein AL, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. *Am J Surg Pathol*. 2010;34:e35-e48.

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