Review Article

Epstein-Barr virus-associated lymphoproliferative disorders in immunosuppressed patients

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Abstract: A diverse range of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (LPDs) arise in the context of immunodeficiency. Post-transplant lymphoproliferative disease (PTLD) encompasses multiple disease entities which develop due to iatrogenic immunosuppression necessary for organ transplantation, and are frequently EBV-positive. A similar spectrum of lymphoproliferative pathologies, many of which are EBV-associated, occur in non-transplant immunodeficiency states, including those secondary to disease-modifying agents, human immunodeficiency virus (HIV) infection, age-associated immunosenescence, and a wide array of primary immune conditions. Common to each of these disease settings is disruption of the normal immune responses that exert control over EBV, permitting the virus to contribute to tumourigenesis. In this review, we provide an overview of the classification of EBV-positive immunodeficiency-associated LPDs, highlighting the strengths and weaknesses of systems provided by the World Health Organisation (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues in comparison to the Society for Hematopathology (SH) and the European Association for Haematopathology (EAH). As an exemplar of EBV-associated LPD, we then undertake a detailed review of the pathophysiology and management of PTLD. This includes a discussion of prophylactic, pre-emptive and therapeutic approaches, recognising important differences in the management of PTLD arising after haematopoietic stem cell and solid organ transplantation. We summarise recent published clinical data guiding the use of conventional chemo-immunotherapy, and cover the role of cellular and novel drug therapies. Thereafter, we provide focused reviews on a selection of other noteworthy EBV-positive LPD entities, highlighting current and emerging strategies for their management: EBV-positive mucocutaneous ulcer, EBV-positive diffuse large B-cell lymphoma, plasmablastic lymphoma, primary effusion lymphoma and lymphomatoid granulomatosis.

Keywords: Epstein-Barr virus (EBV); lymphoma; post-transplant lymphoproliferative disease (PTLD); transplantation; immunodeficiency

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Classification

The World Health Organisation (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues categorises immunodeficiency-related lymphoproliferative disorders (LPDs) into four broad categories, amongst which Epstein-Barr virus (EBV)-associated pathologies feature prominently (*Table 1*) (1). The category of 'LPDs associated with primary immune disorders' includes disease entities that arise in the context of a multitude of rare

Table 1 Immunodeficiency-associated lymphoproliferative disorders, as categorised in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Lymphoproliferative disease associated with primary immune disorders
Lymphomas associated with HIV infection
Post-transplant lymphoproliferative disorders
Non-destructive PTLD
Polymorphic PTLD
Monomorphic B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt lymphoma
Plasma cell myeloma
Plasmacytoma
Other
Monomorphic T-cell neoplasms
Peripheral T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma
Other
Classic Hodgkin lymphoma PTLD
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

immune defects, and which are frequently EBV-positive. 'Lymphomas associated with human immunodeficiency virus (HIV) infection' include several EBV-positive subtypes of lymphoma, such as Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma (HIV-associated lymphomas will be reviewed in a separate article in this series). Meanwhile, 'post-transplant lymphoproliferative disorders' (PTLD) encompasses a spectrum of LPDs which arise in the context of iatrogenic immunosuppression necessary for organ transplantation, many of which are EBV-positive (2-4). Finally, the category of 'other iatrogenic immunodeficiency-associated disorders' includes a similar spectrum of LPDs which occur in non-transplant iatrogenic immunodeficiency states, resulting from agents such as Methotrexate and TNF-alpha antagonists, typically used as disease-modifying agents in autoimmune conditions. Common to each of these disease settings is disruption of the normal immune responses that exert control over EBV, permitting the virus to contribute to tumourigenesis.

The WHO classification categorises immunodeficiency-associated LPDs primarily based on the clinical settings in which they arise, recognising that therapeutic options may vary accordingly. However, there are several drawbacks with this approach. Thus, it somewhat arbitrarily separates LPDs based on clinical context, ignoring that LPDs which arise in different settings nonetheless often share common oncogenic, biologic, and histologic features. It also results in the use of different terminology or diagnostic criteria for essentially identical LPDs arising in different settings. Furthermore, LPDs which develop in less-well characterised immunodeficiency states, such as immunosenescence, are not recognised. To overcome these problems, a new three-part unifying nomenclature has recently been proposed by the Society for Hematopathology (SH) and the European Association for Haematopathology (EAH) (5). In this schema, the first part of the nomenclature comprises the name of the lesion, as per the WHO 2017 classification; the second part comprises the associated virus, such as EBV, if any; and the third part comprises the underlying immunodeficiency. This approach has the advantage of grouping lesions together that share histopathological and biological features, whilst also recognising differences between immunodeficiency states.

In keeping with the SH/EAH classification system, an overview of the four principal pathological categories of EBV-positive immunodeficiency-associated LPDs follows. A more detailed discussion of selected disorders is then provided in the subsequent sections.

EBV-positive B-cell hyperplasias

These lesions arise early in the course of immunodeficiency and are labelled 'early lesions' in the WHO 2008 classification, later amended to 'non-destructive PTLD' in the 2017 revision. They are benign B-cell proliferations that often involve nodal regions, and are non-destructive, with preservation of underlying tissue architecture. They are typically polyclonal, although small clones or simple karyotypic abnormalities may occasionally be detected. Three histologic subtypes are recognised in the WHO 2017 classification: follicular hyperplasia, infectious mononucleosis-type hyperplasia and plasmacytic hyperplasia. In the absence of EBV-association, they can be histologically indistinguishable from other reactive conditions seen in immunocompetent individuals. However, the presence of EBV, as determined by *in situ* hybridisation for EBV-encoded small RNAs (EBERs) or

immunohistochemistry for EBV latent proteins, should alert to the possibility of underlying immunodeficiency. Apart from occurring in the post-transplant setting, they can be seen in other iatrogenic immunodeficiency states and sometimes in the context of age-related immunosenescence (6). The lesions almost always regress, either spontaneously or on correcting immunodeficiency where this is feasible. Their progression to aggressive lymphomas is rare. Surgical resection, typically undertaken for diagnostic purposes, or simple observation, are other management options. It is important to recognise these entities and avoid over-treating.

EBV-positive polymorphic B-cell LPDs

These are destructive lesions which efface tissue architecture. Their morphology spans all stages of B-cell development, with a polymorphous infiltrate, prominent plasma cell differentiation and the presence of immunoblasts and Hodgkin and Reed/Sternberg (HRS)-like cells. Underlying immunodeficiency must be suspected in the presence of typical histology, even if one is not readily apparent. Clonal immunoglobulin (Ig) gene rearrangements are often observed. Most cases regress after withdrawing immunosuppression where this is feasible, or after initiating highly active antiretroviral therapy (HAART) in the case of HIV infection. Surgical resection, radiotherapy or the anti-CD20 antibody Rituximab are therapeutic options for some patients, but chemotherapy is usually not required.

Indolent B-cell lymphomas

These are often EBV-positive small B-cell lymphomas, with characteristic plasmacytoid differentiation. Nodal and extranodal marginal zone lymphomas are the most common type, and these frequently exhibit cutaneous involvement. Lymphoplasmacytic lymphoma and extraosseous plasmacytomas are also described. Morphologically, there is significant overlap with polymorphic B-cell LPD and they are probably best managed on similar lines.

Aggressive B-cell lymphomas

Immunodeficiency-associated aggressive B-cell lymphomas include DLBCL, Burkitt lymphoma, plasmablastic lymphoma (PBL) and classical Hodgkin lymphoma. In some cases, a T-cell and histiocyte rich background may present morphologic features that overlap DLBCL, classical Hodgkin lymphoma and EBV-positive mucocutaneous ulcer (EBV MCU). EBV association is variable. In the post-transplant setting, these entities are grouped under monomorphic PTLD in the WHO classification. Outside of the transplant setting, underlying immunodeficiency may not be suspected in the absence of EBV-association. Historically, they have been treated using similar strategies to those used for the corresponding lymphoma in immunocompetent individuals.

PTLD

PTLD comprises a paradigm in the field of EBV-positive immunodeficiency-associated LPD. From the biological perspective, it is notable that almost any of the histopathological entities of EBV-positive LPD may arise in the iatrogenic state of immunocompromise that follows transplantation. Moreover, due to an ever-increasing trend in the utilisation of transplantation, PTLD is becoming an increasingly common problem, and therefore it has recently attracted a growing degree of research interest.

Pathophysiology

In healthy individuals, EBV establishes lifelong latent infection within resting memory B-cells and is controlled by potent virus specific T-cell responses. However, EBV-specific immune responses are impaired in the iatrogenic state of T-cell immunocompromise that accompanies transplantation. Following solid organ transplantation (SOT), this occurs as a consequence of immunosuppressive drugs which are taken indefinitely to prevent alloreactive immune responses which cause organ rejection (7) but which also put patients at risk of a range of opportunistic infections (8) and malignant complications (9). Commonly used agents are the calcineurin inhibitors Cyclosporin and Tacrolimus, the purine analogue Azathioprine and the inosine monophosphate dehydrogenase-inhibitor Mycophenolate mofetil. Glucocorticoids are also commonly used as adjunctive therapy to treat episodes of threatened organ rejection. EBV-specific T-cell responses are reduced in SOT patients taking even relatively low levels of immunosuppressive therapy (10,11). After allogeneic haematopoietic stem cell transplantation (allo-HSCT), a temporary but profound state of immunocompromise results from conditioning agents given at the time of the transplant to ablate the recipient bone marrow and immune system, as well as immunosuppressive agents including

Cyclosporin and Tacrolimus which are typically delivered for 3 to 6 months post-transplant to prevent graft-versus-host disease. EBV-specific T-cells are absent, or significantly reduced, for at least 6 months following allo-HSCT (12,13).

Consequent upon the impairment of EBV-specific T-cell responses, latently infected B-cells may exhibit opportunistic virus-driven expansion. In asymptomatic patients a subclinical degree of lymphoproliferation may be detected as accumulation of viral DNA circulating in blood, as measured by polymerase chain reaction (PCR) (14) (otherwise known as 'EBV DNAemia' or 'EBV reactivation' in previously seropositive patients). Asymptomatic transplant recipients may also shed increased levels of EBV into the throat (11). However, in a proportion of patients lymphoproliferation occurs to a pathological degree, resulting in the development of PTLD. Following SOT, PTLD occurs most commonly during the first year, although the disease can develop any time after transplant, in some cases after decades (15). However, after allo-HSCT, almost all cases occur within the first 6 months, peaking in incidence at around 2-3 months, with cases rarely occurring beyond 12 months (16). After SOT, the majority of lesions are derived from B-cells of recipient origin, although cases of donor-derived PTLD also occur; these are more common after liver or lung allografts, and frequently involve the donor organ (17-20). In contrast, almost all tumours are derived from B-cells of donor origin after allo-HSCT, although recipient-derived tumours have been rarely reported (21-23). These patterns reflect differences in the biology of these transplant settings, as relatively few donor B-cells are transferred to the recipient during the course of SOT, and host B-cells are usually ablated by conditioning chemotherapy during allo-HSCT.

PTLD displays marked pathological heterogeneity, encompassing all of the pathological subtypes of immunodeficiency-associated LPD outlined above. However, in clinical practice the majority of cases are CD20-positive monomorphic B-cell lymphomas that resemble DLBCL or polymorphic lesions characterised by a spectrum of B-lymphoid cell types (1,24). The DLBCL subtype of PTLD exhibits histology typical of that occurring in immunocompetent individuals, but with variable positivity for EBV, ranging from 50–60% in most studies. The lesions invariably have monoclonal Ig rearrangements. Most arise from either germinal centre (GC) or post-GC B-cells (25,26), with the majority of lesions displaying an activated B-cell (ABC) phenotype. Analysis of viral gene expression in EBV-positive B-cell PTLD tumour specimens typically reveals the Latency III pattern, in which all viral latent genes are active (27). It is through this pattern of expression that EBV exerts its transforming effects on B-cells in vitro, causing virus-driven cellular proliferation in lymphoblastoid cell lines, and contributes to the tumorigenesis of PTLD *in vivo*. However, a proportion of B-cell PTLD tumours exhibit more restricted forms of latent viral gene expression, and heterogeneity can also be found within individual lesions (28-30). Studies to investigate the genetic landscape of PTLD, whilst not identifying a characteristic mutational signature, have revealed an increased frequency of mutations in monomorphic cases, in those occurring later after transplant, and in EBV-negative lesions (31-36).

The clinical presentation of PTLD can be highly variable but it commonly involves systemic features including fever, sweats and weight loss (B-symptoms) (24), sometimes accompanied by a sore throat similar to that observed in acute IM, and lymphadenopathy. Other potential manifestations include encephalitis, hepatitis or a fulminant sepsis-like picture that rapidly leads to multi-organ failure, particularly after allo-HSCT. A high incidence of extranodal disease is observed, with involvement of the gastrointestinal tract occurring most frequently. Disease affecting the transplanted organ is also relatively common. Established PTLD has conventionally been associated with high rates of mortality, and on occasions it is diagnosed post-mortem, highlighting the need for vigilance and early recognition.

The reported incidence of PTLD varies from <1% up to 10% in most studies, although rates are highly variable with regard to host- and transplant-related risk factors. For PTLD arising after SOT, the intensity of iatrogenic immunosuppression, and in particular the degree of T-cell suppression, is a fundamental determinant of PTLD risk. The cumulative level of immunosuppression is likely to be more important than the individual immunosuppressive agents used, as studies seeking to compare drugs have generated conflicting data (37). However, agents that specifically deplete T-cells, such as the anti-CD3 monoclonal antibody OKT-3 and anti-thymocyte globulin (ATG) have been associated with a particularly high incidence of disease (15,38-42). Patients undergoing cardiothoracic or intestinal transplants are also at greater risk than those receiving liver or renal transplants, consistent with the requirement for more intensive immunosuppression with the former (15,39,43-45). Interestingly, the incidence of lymphoma in renal transplant patients who lose their graft and

subsequently cease immunosuppression reverts to pre-transplantation levels (46). Importantly, negative EBV serological status at the time of transplant is a major risk factor for PTLD, and incidence is increased further when SOTs are derived from an EBV seropositive donor (39,46-49). For example, Ho *et al.* reported a 20-fold higher incidence in PTLD amongst EBV seronegative SOT recipients (49). This reflects the consequence of undergoing primary EBV infection in the context of immunocompromise. Furthermore, it explains the elevated risk of PTLD, and shorter intervals from transplant to disease onset, observed amongst paediatric solid transplant recipients (15,50). Risk factors specific to the allo-HSCT setting are principally related to the degree of graft T-cell suppression (16,21,51-63). Thus, whereas T-cell replete transplants rarely develop PTLD, graft T-cell depletion using ATG or the anti-CD52 monoclonal antibody Alemtuzumab is associated with a significantly increased incidence of PTLD. Of these agents, Alemtuzumab confers a lower risk than ATG presumably because it also eliminates B-cells from the donor graft (16,51). Other risk factors are unrelated and/or HLA-antigen-mismatched donors, the occurrence of acute or chronic GvHD, increasing age at transplant and re-transplantation (16).

Management

Given a lack of prospective randomised controlled studies, the management of PTLD has been predominantly informed by a limited number of non-randomised prospective series, retrospective datasets, and expert opinion. Differences between the SOT and allo-HSCT settings necessitate tailored management strategies, and this is reflected in the following discussion.

Pre-transplant screening of recipient and donor EBV serostatus facilitates the identification of high-risk seronegative recipients. This provides the opportunity to avoid T-cell depleting agents in these patients, and allows selection of a seronegative donor, where possible. Although there are currently no accepted prophylactic treatments for PTLD, Rituximab in the pre- or peri-transplant period may reduce the risk of post-transplant EBV reactivation in high-risk situations such as T-deplete allo-HSCT (64,65) or multi-visceral SOT (66). In the setting of allo-HSCT, infusions of EBV-specific cytotoxic T-cells generated from transplant donors have been successfully used to reduce the risk of PTLD in paediatric patients (67), although this strategy has not been adopted widely.

Patients with EBV-associated PTLD develop high levels of circulating EBV DNA, therefore EBV qPCR monitoring has been evaluated as means to identify patients with impending PTLD. This affords the opportunity to intervene 'pre-emptively', by reducing the patient's immunosuppression to facilitate recovery of endogenous EBV-specific T-cell responses and/or by administering Rituximab, which effectively depletes B-cells and which can prevent or treat PTLD (68). However, in the SOT setting, evidence to support EBV qPCR monitoring and pre-emptive management is limited - many otherwise asymptomatic patients develop transiently raised EBV loads after SOT, and some patients exhibit chronically elevated levels, with no clear relationship to the development of PTLD. Consequently, current guidelines do not support the routine use of EBV qPCR monitoring for SOT patients, except for recipients of cardiothoracic or intestinal transplant who are at particularly high risk due to the depth of immunosuppression required (24,69), and in cases where an EBV-seronegative patient receives an organ from a seropositive donor. If monitored patients develop raised EBV loads, pre-emptive management should be instituted, involving thorough clinic-radiological assessment to search for evidence of PTLD and reduction of immunosuppression (RI). However, the routine use of pre-emptive Rituximab therapy is not currently supported for SOT recipients.

In the setting of T-cell deplete allo-HSCT, in contrast to SOT, EBV DNA monitoring and pre-emptive therapy with Rituximab and RI is widely accepted as the current standard of care. Reflecting this, guidelines from the Second European Conference on Infections in leukemic have advocated EBV qPCR monitoring for all patients undergoing high risk allo-HSCT (principally defined as unrelated, HLA-mismatched or T-cell deplete transplants), with weekly testing for at least 3 months after transplant (70). It is advised that patients who develop high-level EBV DNAemia should receive pre-emptive treatment comprising Rituximab and RI where feasible. Several retrospective studies have shown this approach to be effective, resulting in lower rates of PTLD when compared to historic patient cohorts (71-74). For example, in a series of 38 patients with high-level EBV reactivation occurring after T-cell deplete allo-HSCT, the response rate to pre-emptive Rituximab was 92%; 30 patients without PTLD, and 5 of 8 (63%) with evidence of PTLD on imaging at treatment initiation, achieved complete response (CR) to Rituximab (64).

For patients with established PTLD after SOT, first-

line management typically includes RI. However, this is frequently inadequate to produce sustained remission and exposes patients to the hazards of organ rejection. Meanwhile, no role for pharmacological antiviral therapies is currently supported by existing data (75). Instead, upfront therapy for B-cell PTLD relies on the use of Rituximab, given either as monotherapy or in combination with cytotoxic chemotherapy, typically CHOP (Rituximab plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone). Rituximab monotherapy, comprising at least 4 infusions, was previously examined as first-line therapy for PTLD in a small number of prospective studies (76-79). These showed it to be well tolerated and delivered ORRs of 44–79%. However, durable remissions were achieved in less than half of these unselected patients (76-79). Meanwhile, several retrospective series reported better and more durable responses with anthracycline-based chemotherapy, principally with CHOP-like regimens (80-83). However, concerns have been raised about unacceptable toxicity with upfront use of CHOP in patients with PTLD. Thus, in a retrospective study by Choquet *et al.* treatment-related mortality (TRM) was reported as 31% amongst 26 patients treated with CHOP-21 (84). Meanwhile, in a retrospective analysis by Elstrom *et al.* TRM was 26% amongst 19 patients treated with CHOP or R-CHOP (81).

Given the concerns about toxicity related to CHOP, a strategy involving upfront treatment with four weekly infusions of Rituximab for all patients, delivered with the aim of improving performance status and tolerability, before escalating to 4 cycles of CHOP-21, was introduced by Trappe *et al.* This protocol of sequential immuno-chemotherapy was initially evaluated in 70 patients in the phase II PTLD-1 study, which demonstrated an ORR of 60% following Rituximab monotherapy, rising to 90% after CHOP, with a median OS of 6.6 years (85). The PTLD-1 trial protocol was thereafter amended to incorporate response-stratified treatment, such that patients who achieved CR after four infusions of Rituximab were consolidated with four additional three-weekly infusions of Rituximab instead of chemotherapy (86), whereas those with less than CR received four cycles of R-CHOP-21. The second part of the trial (PTLD-1/3) treated 174 patients, delivering outcomes similar to those of the first part, with an ORR of 88% and median survival of 6.6 years, but 25% of the cohort avoided cytotoxic chemotherapy. As the largest prospective study delivered in PTLD, and with the demonstration that a response-stratified approach can facilitate chemotherapy-free cure in a quarter of patients, this approach is now regarded by many clinicians as the current standard of care in the treatment of PTLD after SOT. Support for Rituximab monotherapy as initial treatment also comes from a recent retrospective series which compared outcomes amongst 101 patients treated upfront with either Rituximab monotherapy or R-CHOP (87). Although there was a non-significant trend toward improved responses with R-CHOP, with ORR of 75% versus 90%, and CR of 53% versus 71%, for the treatments respectively, this did not translate into improved OS or progression-free survival (PFS), which were similar between the groups. Notably, an excess of non-PTLD mortality was not observed in those treated with R-CHOP. An important drawback of the study is that choice of upfront treatment was made by treating physicians, such that patients may have been preferentially assigned to either Rituximab or R-CHOP depending on the perception of risk. But despite this limitation, the authors conclude that upfront Rituximab therapy should be the preferred option for most patients.

A number of baseline prognostic factors have been proposed for PTLD arising after SOT (88-91). However, more recently the International Prognostic Index (IPI) for DLBCL has emerged as a useful prognostic tool (87,92). For example, in a large retrospective series, the 3-year OS was 78% and 54% for patients with low (IPI 0-2) versus high-risk IPI (IPI 3–5) respectively (87). Baseline IPI has now been incorporated into a risk-adapted treatment strategy in both the PTLD-2 trial, and the UK National Cancer Research Institute Phase II 'TIDaL' study (EudraCT 2015-005454-35) which is currently examining the Bruton's tyrosine kinase (BTK) inhibitor Ibrutinib in combination with Rituximab in upfront treatment of PTLD. In both studies, patients are considered to be at low risk of progression if they achieve either CR after 4 weekly doses of Rituximab (along with Ibrutinib in the TIDaL trial) or partial remission (PR) if they have low-risk IPI (IPI 0–2) at baseline. These low-risk patients subsequently complete treatment with four further doses of Rituximab (plus Ibrutinib in TIDaL) every 21 days, thereby avoiding chemotherapy. In an interim analysis of the PTLD-2 trial, adopting this strategy increased the proportion of patients who avoided chemotherapy to 33%, compared to 25% in the PTLD-1/3 study (93).

Unfortunately, a significant proportion of patients with PTLD remain either refractory to frontline immuno-chemotherapy or subsequently relapse, and the outcomes for these patients with conventional treatment is typically

poor. Thus, effective salvage options for PTLD after SOT are limited, with no good evidence to support use of intensive chemotherapy or stem cell transplantation. Meanwhile, the management of patients after allo-HSCT who fail to respond to Rituximab is challenging, with extremely disappointing outcomes associated with cytotoxic chemotherapy, with up to 100% mortality (4,94). For these patients, the most promising therapeutic option to emerge in recent years is adoptive cell therapy. In the allo-HSCT setting, one form of this treatment involves the administration of transplant donor-derived unselected donor lymphocyte infusions (DLI), which contain EBV-specific T-cells whenever the donor is EBV-seropositive. By reconstituting virus-specific immunity and effecting anti-tumour responses, these have been used as successful salvage therapy for established PTLD, with response rates of around 70% (95-98). However, this approach is limited by the risk of alloreactive T-cell responses, which may result in potentially life-threatening graft-versus-host disease. Alternatively, *in vitro* preparations of EBV-specific T-cells (EBV-CTLs) can be generated by stimulating donor or third-party lymphocytes, to avoid this complication. These have been used effectively, both as prophylaxis and in the treatment of established PTLD, with response rates similar to those achieved with DLI and without evidence of alloreactivity (67,72,99,100). Furthermore, in order to circumvent delays of several months associated with the use of autologous preparations, cryopreserved banks of third party EBV-CTLs have been generated, from which partially HLA-matched EBV-CTLs can be accessed at short notice (100,101). This approach was originally investigated by Haque at al. in a prospective phase II study in which 33 patients with progressive PTLD (31 of whom were SOT recipients) were treated with cryopreserved third party EBV-CTLs (100). No hypersensitivity or alloreactive responses were observed and an ORR of 52% at 6 months was observed. In a long-term follow-up report, 12 of 14 patients who achieved CR remained alive and free of disease after 4–9 years (102). The same group have recently reported outcomes amongst 59 patients treated with EBV-CTLs from their second-generation bank. The ORR for the entire cohort was 59%, with 39% of patients achieving CR. Patients treated after SOT had improved outcomes compared to those after allo-HSCT patients, with an ORR of 75% and 3-year OS of 60%. Notably, 24 of 59 patients had central nervous system (CNS) involvement, and these had excellent responses to CTL therapy, with an ORR of 67% and 3-year OS of 50% (103). In another recently reported series, the ORR and 1-year OS was 68% and 89% for patients after allo-HSCT, and 54% and 82% for those after SOT (104).

Regarding future directions in the management of PTLD, the role of novel agents remains to be elucidated. Ibrutinib shows preferential activity for the post-GC ABC subset of immunocompetent DLBCL which most PTLD lesions also exhibit, and as already mentioned above, this is currently being investigated in the TIDaL study. B-cell PTLD tumours frequently express programmed cell death-1 (PD-1) and PD-1 ligand-1 (PD-L1) (105), and therefore checkpoint inhibitors may be a potential therapeutic option, although risk of causing organ rejection may preclude their use. CD30 is frequently expressed in B-cell PTLD and therefore targeting this may be an attractive option. A recent trial examining the anti-CD30 monoclonal antibody-drug conjugate Brentuximab vedotin in combination with Rituximab showed efficacy, although tolerability was a limiting factor (106). A strategy involving induction of EBV lytic antigen expression with histone deacetylase inhibitors and subsequent targeting with antiviral drugs was previously explored in a small study which used a combination of Arginine Butyrate and Ganciclovir, with encouraging responses (107). Unfortunately, EBV-CTLs are still not universally available, due in part to the laborious and costly nature of their production. However, novel approaches are seeking to address this issue, including *ex vivo* selection of virus-specific T-cells (108-110) or genetically engineered T-cells (111). Notably, CD19-directed chimeric antigen receptor (CAR) T-cell therapy has recently been approved for the treatment of relapsed or refractory DLBLC, although this treatment presents challenges in the context of transplantation. Patients taking immunosuppressants because of a transplant, by definition, have functional T-cell deficiency which may affect the quality of the CAR T-cell product. Additionally, immunosuppression can interfere with the proliferation of CAR T-cells after infusion. There are also concerns about the risk of graft rejection. In a recent small series, outcomes for patients with PTLD treated with anti-CD19 CAR T-cells were disappointing, revealing excessive toxicity (112).

Other EBV-associated LPDs

Notwithstanding the broad spectrum of diseases that exist under the umbrella of EBV-positive immunodeficiency-associated LPD, in the present section we have selected several entities, principally identified by their

histopathological characteristics, that we regard as particularly noteworthy. They have been selected by merit of their specific disease characteristics and the strategies used to treat them, rather than by any particular classification system.

EBV-positive mucocutaneous ulcer

EBV-positive mucocutaneous ulcer (EBV MCU) is a relatively recently described entity which shares histologic features with polymorphic LPD and which can also mimic classical Hodgkin lymphoma or aggressive B-cell lymphomas (113). It has typically been described in elderly patients, where age-related immunosenescence is thought to be contributory, and in iatrogenic immunodeficiency, especially related to use of Methotrexate. However, EBV MCU can be seen in a variety of immunodeficiency states. Clinically, EBV MCU presents as well-circumscribed ulcers, which are often painful, involving mucosal or cutaneous sites. Most lesions are self-limiting or regress upon withdrawal of immunosuppression, although they sometimes follow a remitting-relapsing course. Rituximab (114) or radiotherapy are useful treatment options for some patients.

EBV-positive diffuse large B-cell lymphoma, not otherwise specified

Although EBV-positive DLBCL, not otherwise specified (EBV-positive DLBCL NOS) is now recognised as a distinct entity in the WHO classification (1), it was initially described in elderly patients in whom it carried a poor prognosis, and where it was thought to be associated with age-related immunosenescence because of similarities with other immunodeficiency-associated lymphomas (115,116). Since the original reports, this condition has since been reported in younger, apparently immunocompetent patients (117-119).

The tumours exhibit a morphologic continuum from polymorphic lesions, where large B-cells are scattered amongst a T-cell and histiocyte rich infiltrate reminiscent of T-cell rich B-cell lymphoma, to monomorphic lesions where there is a diffuse pattern of large B-cells (1,120). However, morphologic subtypes have no prognostic relevance. The large cells may resemble centroblasts, immunoblasts or even HRS cells, and express B-cell markers, with CD30 expression also observed in about 40% of cases. The tumours typically display a latency III pattern of EBV gene expression (121), which is a feature of immune dysregulation, although cases described in younger patients can show a more restricted latency II pattern (118). Most exhibit an activated B-cell phenotype, expressing MUM1/IRF4, NF-κB and phosphorylated STAT3. Clonally rearranged Ig genes are found in about 60% of cases (122). Gene expression profiling shows EBV-positive DLBCL to be distinct from EBV-negative DLBCL, with enhanced signalling through toll-like receptor and JAK-STAT pathways (123). PDL1 expression on tumour cells or in the microenvironment (mPDL1) is almost always seen in EBV-positive DLBCL, compared to 10–15% of EBV-negative DLBCL where it is associated with an inferior prognosis.

The treatment of EBV-positive DLBCL is similar to its EBV-negative counterpart, with R-CHOP being the current standard of care. However, response rates and survival are worse compared to EBV-negative DLBCL in most series (116,117,124-128). Clinical factors predicting for poor outcome include age >70 years, presence of B-symptoms (116), advanced stage, and absolute lymphocyte count of $<1.0\times10^9$/L (129). Other factors predicting for poor prognosis in EBV-positive DLBCL include CD30 expression (123), expression of survivin (a member of the inhibitor of apoptosis protein family) on tumour cells (130) and high serum survivin levels (127). Novel treatment strategies currently under evaluation include checkpoint inhibition, anti-CD30 antibodies, and cellular therapies comprising EBV-CTLs or CD-19-directed CAR-T cells.

Plasmablastic lymphoma

Though initially reported in HIV-positive patients (131), PBL is also seen in other immunodeficiency states, as well as in patients with no apparent immunodeficiency (132), although most of the latter are either elderly with probable age-related immunosenescence or have other conditions associated with a certain degree of immunosuppression (133). Median age at diagnosis is 50 years, with HIV-negative patients being older, in keeping with the possibility that age-related immunosenescence may be contributory (132,134). There is a significant male preponderance, with around 75% of reported cases occurring in men. The disease typically presents at an advanced stage at extranodal sites, with frequent involvement of the oral cavity, gastrointestinal tract, skin, and marrow, whilst nodal disease is less common.

Histologically, PBL is characterised by tumour cells displaying immunoblastic morphology, with a phenotype of terminally differentiated B-cells to plasma cells, expressing

CD79a, CD38, CD138, IRF4/MUM1, Blimp1, and XBP1. Expression of B-cell markers such as CD19, CD20 and PAX5 is lost (135). EBER expression is seen in around 70% of cases and is more frequent in HIV-positive and post-transplant PBL. EBV gene expression is usually latency I, although latency III can be seen in HIV-positive or post-transplant cases (135). Amplification and translocation of the MYC oncogene, frequently involving an Ig gene partner, and overexpression of MYC protein are common (136-138). Recurrent somatic mutations in PRDM1 are found in about 50% of cases, resulting in impaired BLIMP1 protein expression and contributing to the oncogenicity of MYC (139).

The prognosis of PBL is generally extremely poor, with median survival of <12 months. The IPI may have prognostic value (133,140). Patients presenting with limited stage disease may have good outcomes with aggressive combination chemotherapy and radiotherapy (141). There is no accepted standard chemotherapy regimen for PBL. CHOP is the most widely used combination but more intensive regimens such as Hyper-CVAD/MA (hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin and Dexamethasone/high-dose Methotrexate and Cytarabine), CODOX-M/IVAC (Cyclophosphamide, Vincristine, Doxorubicin and Methotrexate/Ifosfamide, Etoposide and Cytarabine), or infusional EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin) are all used. Between 50–66% of patients attain CR, which confers a better prognosis. However, it remains unclear if the more intensive regimens confer a survival benefit (142,143). Though data is very limited, for patients who are fit and have chemosensitive disease, there appears to be some benefit from high dose chemotherapy and autologous stem cell transplant consolidation in first remission, especially for those with high-risk disease (133,142,144,145).

Bortezomib and Lenalidomide have also been used in PBL, given its similarity with multiple myeloma, but data is very limited. Addition of Bortezomib to dose-adjusted EPOCH (DA-EPOCH) chemotherapy has been reported with encouraging outcomes (146,147). PBL consistently expresses CD38, therefore the anti-CD38 monoclonal antibody Daratumumab may be another potential therapy to explore. High levels of PD-1 and PD-L1 expression have been reported in PBL, especially in EBV-positive cases (148), suggesting a potential role for immune checkpoint inhibitors in its management. The role of EBV-CTLs in EBV-positive PBL has not yet been evaluated.

Primary effusion lymphoma

Primary effusion lymphoma (PEL) is a disease which affects middle-aged individuals with an underlying immunodeficiency. It is typically seen in HIV-positive patients but has also been described in several other immunocompromised conditions. Clinically, it presents as a malignant lymphomatous effusion affecting the body cavities (the pleural space, pericardial space or peritoneal cavity) (149,150), often accompanied by prominent B-symptoms. Rarely it presents with an extracavitary mass. PEL is consistently associated with Human Herpesvirus 8 (HHV-8) infection, which is implicated in its pathogenesis (151). However, EBV co-infection is seen in 60–90% of cases, although the role of EBV in the pathogenesis of PEL is not clear (150,152,153). Diagnosis is made by examination of cells in the effusion fluid. PEL cells show variable morphology, ranging from immunoblastic or plasmablastic to anaplastic. The cells are positive for CD45 and the plasma cell markers CD38 and CD138, but lack the B-cell markers CD19, CD20 and CD79a. There is universal expression of the HHV8-asociated protein LANA1 in the nuclei, which is useful for diagnosis (1). Treatment is often with combination chemotherapy, using CHOP or DA-EPOCH. However, many patients are not fit for intensive chemotherapy due to poor performance status or comorbidities, and these patients have an extremely poor prognosis. HIV-positive patients should receive HAART.

Lymphomatoid granulomatosis

LYG is a rare EBV-associated B-cell LPD with unique clinical and pathological features that distinguish it from other EBV-associated LPDs (154). It is typically seen in apparently immunocompetent individuals, with no known pre-existing immunodeficiency. However, upon careful evaluation, signs of immune dysfunction can be detected in most patients, with alteration of immune cell subsets and defective immune surveillance of EBV-infected B-cells (155-157). Pathologically, LYG is characterised by the presence of atypical EBER-positive B-cells within a background of prominent polymorphous inflammatory infiltrate, comprising T-cells, plasma cells and histiocytes associated with angioinvasion, angiodestruction and coagulative necrosis (158). Histologically, LYG is classified as low grade (grades 1 and 2) or high grade (grade 3) based

on the number and frequency of EBER-positive B-cells. Histological grade correlates with clonality, with clonal rearrangement of Ig genes being more frequent in high grade disease (158), and this likely represents transformation of EBV-infected B-cell clones (154).

LYG is typically seen in middle age adults, with a male preponderance of 2:1. It presents at extranodal sites, with universal lung involvement. Other common sites include the skin, CNS, kidneys and liver. Marrow and nodal involvement are rare (158-162). Pulmonary imaging often shows multifocal nodular masses, sometimes with central necrosis and cavitation. Skin lesions may present as indurated plaques or nodules, with or without ulceration (163,164). CNS involvement may manifest as multifocal parenchymal brain lesions or abnormal enhancement of the leptomeninges and cranial nerves on magnetic resonance imaging (165).

Historically, LYG has been reported to have poor prognosis, with median survival of less than 12 months (157,159,161). Given that low grade LYG is frequently polyclonal, it can be managed by strategies aimed at augmenting the immune system (155). For some patients with low grade disease, a period of observation may be an option, along with correction of any underlying immunodeficiency where possible. However, most patients eventually require therapy (154). In an ongoing prospective National Cancer Institute study, interferon-α therapy has been reported to produce ORRs of 60%, with CR in more than half of responders (166). Patients with CNS involvement have similar response rates. Responses were generally durable, with 10-year OS and PFS of 64% and 37% respectively. Patients with high grade LYG are treated with chemoimmunotherapy, similar to other aggressive B-cell lymphomas. DA-EPOCH-R (DA-EPOCH with Rituximab) seems active, with ORR and CR of 77% and 41% respectively, and 5-year OS and PFS of 66% and 28% respectively (166). Response and survival with R-CHOP seems to be similar (160).

Patients presenting with low grade LYG often progress to high grade disease, whilst patients with high grade LYG usually relapse with low grade disease following first-line treatment. Patients with low grade LYG who either progress whilst on, or relapse after, interferon-α seem to have good response rates with DA-EPOCH-R. Similarly, patients with high grade LYG refractory to or relapsing after DA-EPOCH-R have good responses to crossover treatment with interferon-α (166). Autologous or reduced-intensity allogeneic HSCT should be considered in patients with multiply relapsed or refractory disease. A retrospective European Society of Blood and Marrow Transplantation (EBMT) series reported outcomes for 10 patients who between them received 9 autologous and 4 allo-HSCT. Six of 10 patients were alive and disease-free after a median follow up of 5.1 years, but TRM was high is this small series (167). Regarding novel therapies for LYG, immune checkpoint inhibition is currently being examined in an ongoing clinical trial (NCT03258567). EBV CTL therapy is another potential therapeutic option which merits further investigation in LYG.

Conclusions

An impressively diverse array of EBV-associated LPDs may arise in immunocompromised patients. However, the WHO and SH/EAH classification systems provide a vital framework to understand these disorders, focusing in turn on the clinical contexts in which they occur, and common pathological features across these settings. Given their rarity, these conditions have historically been managed according to anecdotal evidence or retrospective case series. However, recent progress has been made in terms of prospective clinical trials, particularly for PTLD, which are helping to build an evidence-base to inform management. Furthermore, novel therapies such as anti-CD30 antibodies, BTK and checkpoint pathway inhibitors, and cellular therapies, provide opportunities to deliver improved clinical outcomes in future.

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